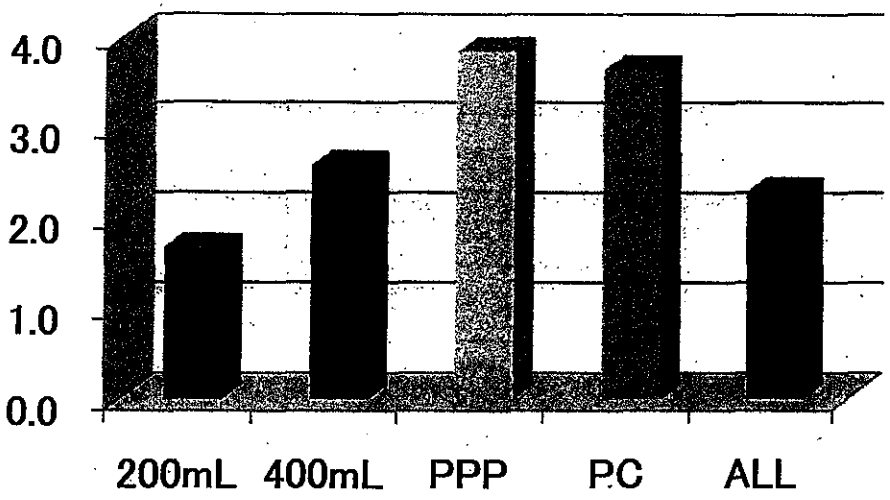
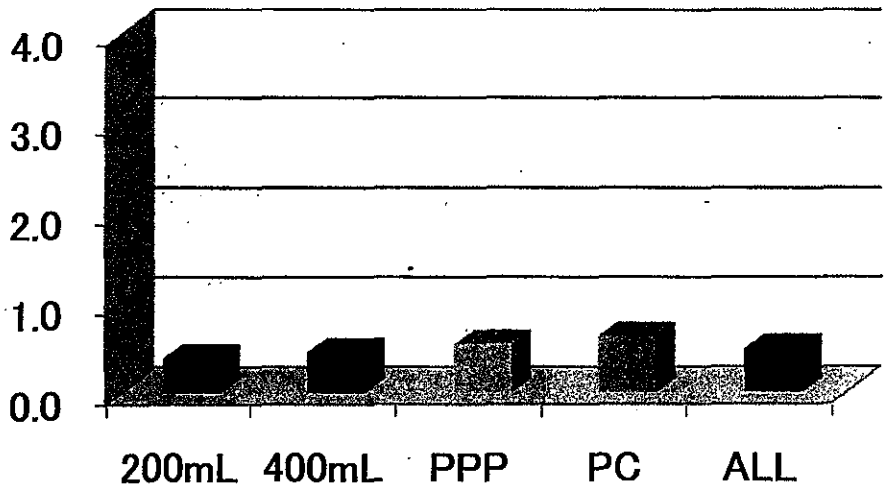
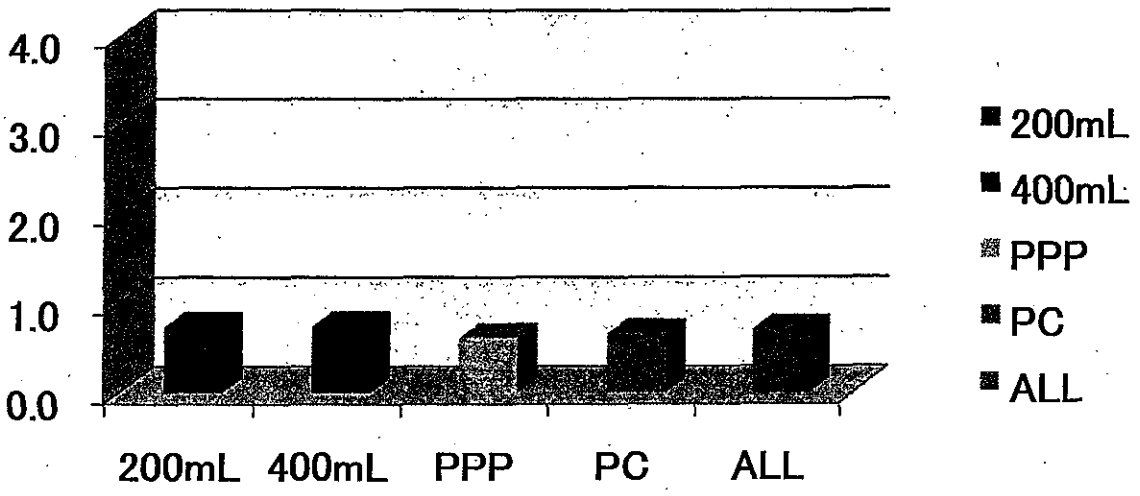
初回VVR発生率(%)



再来VVR発生率（%）



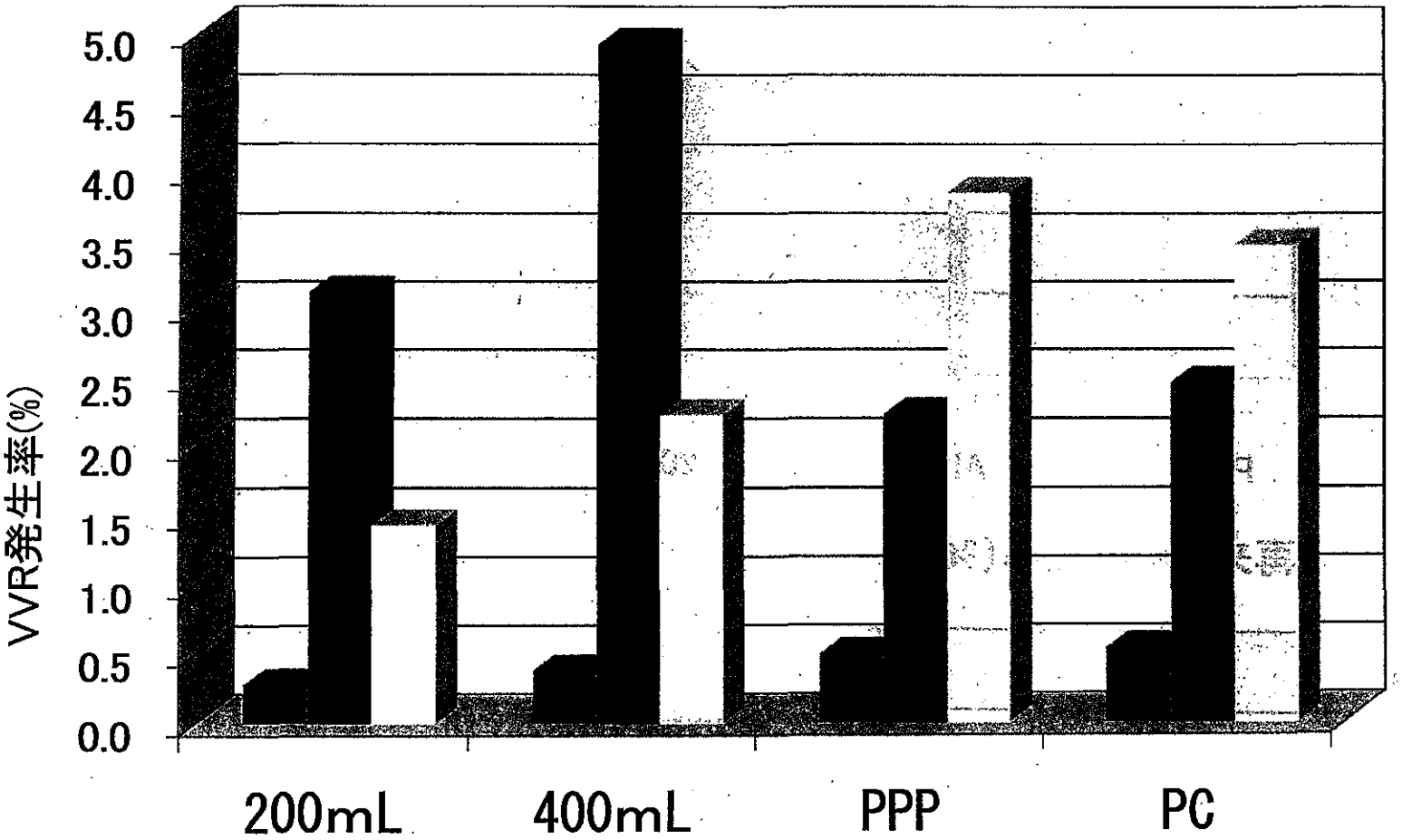
初回再来VVR発生率(%)



平成18年1月～平成18年12月

Japanese
Red Cross Society

初回献血者、VVR歴あり献血者のVVR発生率(%)



	VVR歴なし	VVR歴あり	初回
200mL	0.28	3.13	1.43
400mL	0.38	4.93	2.23
PPP	0.50	2.24	3.85
PC	0.54	2.46	3.48

平成16年10月～平成17年9月

Japanese
Red Cross Society

WHO Technical Report Series, No. 840, 1994

Annex 2
Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (Requirements for Biological Substances No. 27, revised 1992)

Introduction

In 1976, a WHO Working Group on the Standardization of Human Blood Products and Related Substances (*1*) considered the need for international requirements for the processing and control of whole human blood and blood products. It emphasized that, as the quality of the source material played an important part in determining the quality of the final products, such requirements should cover all the stages in the process, from the collection of the source materials to the quality control of the final product. In response to the Working Group's recommendations, the Requirements for the Collection, Processing and Quality Control of Human Blood and Blood Products were published in 1978 (*2*). These Requirements were updated and revised in 1988 (*3*), and WHO recommendations concerning testing for antibodies to human immunodeficiency virus (HIV, *4*) were taken into account. This Annex contains a further revision of the Requirements, applicable to the quality control of blood, blood components and plasma derivatives.

A number of other WHO publications have dealt with whole blood and its components, among them guidelines intended mainly for blood transfusion services (*5*). Guidelines of a more general nature, such as the Guidelines for National Authorities on Quality Assurance for Biological Products, have also been published (*6*). The latter call for a quality-assurance system based on the existence of a national structure that is independent of the manufacturer and is responsible for granting licences for biological products, defining procedures for product release and setting up a post-marketing surveillance system. These Guidelines should be followed by any country having or wishing to set up an organization for the collection and fractionation of blood and blood components.

The names of the many experts who provided advice and data taken into account in this revision of the Requirements are listed in the Acknowledgements section, page 96.

General considerations

The setting up of an organization for the collection and fractionation of human blood and blood components calls for a great deal of expertise and considerable investment. Any country contemplating the establishment of such an organization should carry out a careful cost-benefit analysis to determine whether the investment is justified. A logical developmental sequence for a comprehensive organization starts with the collection and distribution of whole blood, progressing later to the separation of whole blood into components and then the fractionation of plasma pools. It is not always possible to be specific about the details of the procedures employed, the in-process controls or the tests applied at each stage of production, in particular for whole blood and component cells. In addition, although the general principle of fractionation of plasma is well established, there are in practice numerous variations in the details of the various production steps. Therefore, any country wishing to begin the collection and fractionation of blood and blood components should send personnel for training to a plant that is operating successfully. WHO may be able to help in arranging such training.

One of the basic questions to be answered by a country considering whether to start fractionation of plasma is whether there is a suitable donor population of sufficient size to guarantee an adequate supply of source material. It is not possible to set a lower limit for the quantity of source material that would be necessary to make such an operation economic because too many factors are involved. However, in order to maintain competence in production and to avoid certain contamination risks, it is important to have sufficient source material to maintain the fractionation facility in continuous operation.

In a comprehensive organization, the greatest expense is that involved in setting up the fractionation plant, but it is also possible to regard the collection of source material and its fractionation as quite separate operations. A country may wish to establish collection centres for separating the cell components and then send the plasma to an established fractionation plant in another country, from where the products could be returned to the original country. The costs of such an operation might be less than those involved in establishing and operating a fractionation plant.

The general prevalence of certain infectious diseases, such as various forms of hepatitis and parasitic diseases, and of HIV infection differs so markedly in different geographical regions that each national authority must decide for itself whether it is cost-effective to apply the most sensitive test to each blood donation and whether it is feasible to collect suitable source material. A brief protocol for the collection of source material is in any case mandatory (see Appendix). Great emphasis should be placed on the production of fractions by a process that experience has shown results in the least risk of contamination. For example, immunoglobulin prepared by the cold ethanol fractionation method of Cohn has a well established

clinical record of being free from contamination with HIV and hepatitis B virus (HBV), as have albumin products prepared by the same method, stabilized and heated for 10 hours at 60 °C (*5*). Nevertheless, extreme care is required in manufacture to ensure that these products are free from infectious viruses, and it cannot be assumed that different fractionation methods will be equally effective. When a fractionation process is introduced or significant modifications are made to an existing production process, the process or the modifications should be validated or revalidated by appropriate procedures, including the use of marker viruses and, where applicable, special *in vitro* and *in vivo* testing.

Blood can harbour a number of different viruses, and the use of medicinal products derived from human blood has led to transmission of viruses such as HBV and HIV. The risk of virus transmission by blood and blood products can be diminished by the testing of all individual donations. Policies for mandatory testing shall be determined by the national control authority, and should be reviewed regularly and modified according to the current state of knowledge.

Special care and appropriate measures approved by the national control authority must be taken to protect the health of the staff of blood collection and fractionation facilities.

The transport of source materials from blood collecting centres and hospitals to fractionation facilities requires special consideration. Refrigeration at the temperature range appropriate for the product must be efficient and reliable and proved to be so by monitoring. Thermal insulation must provide an adequate safeguard against a temporary failure of refrigeration. Containers of liquid source material should be filled so as to minimize frothing due to shaking. Because of the potentially infective nature of these biological materials, suitable protection should be provided against breakage, spillage and leakage of containers.

In these Requirements, the word "human" has been omitted from the names of products derived from human blood. Products of animal origin are immunogenic, and their administration to humans should be avoided whenever equivalent products of human origin can be used instead. The proper name of any blood product of non-human origin should include the species of origin.

These Requirements consist of four parts:

- Part A. Requirements for the collection of source materials
- Part B. Requirements for single-donor and small-pool products
- Part C. Requirements for large-pool products
- Part D. National control requirements.

Each deals with a separate aspect of collection, processing and quality control, but all the parts are intended to be taken together to constitute a single document. It will not be possible to rely on any blood product unless the relevant requirements for each step are complied with, and any attempt

to make them less stringent may have serious consequences for the safety of the final product.

Parts A-D are divided into sections, each of which constitutes a recommendation. The parts of each section printed in normal type have been written in the form of requirements, so that, if a health administration so desires, they may be adopted as they stand as definitive national requirements. The parts of each section printed in small type are comments or recommendations for guidance.

Should individual countries wish to adopt these Requirements as the basis for their national regulations concerning blood products and related substances, it is recommended that modifications be made only on condition that the modified requirements ensure at least an equal degree of safety and potency of the products. It is desirable that the World Health Organization should be informed of any such changes.

Increasing demand for blood products is resulting in the extensive movement of such products from one country to another. Internationally accepted requirements are therefore necessary so that countries without any regulations on blood products and related substances may refer to them when importing such products.

International Biological Standards and Reference Reagents

Rapid technological developments in the measurement of the biological activity of blood products and related substances require the establishment of international biological reference materials. The first two such materials (for anti-A and anti-B blood-typing sera) were established in 1950, and further reference materials have been established since. A number of materials are currently under investigation for use in the preparation of new standards.

The activity of blood products must be expressed in International Units where an International Standard exists. WHO publishes a list of such standards (revised from time to time and most recently in 1990) under the title *Biological substances: International Standards and Reference Reagents.*

Definitions

The following definitions are intended for use in this document and are not necessarily valid for other purposes.

Blood collection: a procedure whereby a single donation of blood is collected in an anticoagulant and/or stabilizing solution.

Processing: any procedure that takes place after the blood is collected.

Plasmapheresis, apheresis and cytapheresis: procedures whereby whole blood is separated by physical means into components and one or more of them returned to the donor.

Closed blood-collection and processing system: a system for collecting and processing blood in containers that have been connected together by the manufacturer before sterilization, so that there is no possibility of bacterial or viral contamination from outside after collection of blood from the donor.

Donor: a person who gives blood or one of its components.

Single-donor materials

Whole blood (sometimes referred to as "blood"): blood collected in an anticoagulant solution with or without the addition of nutrients such as glucose or adenine. Whole blood is collected in units of 450 ml.

Blood component: any part of blood separated from the rest by means of physical procedures.

Plasma: the liquid portion remaining after separation of the cellular elements from blood collected in a receptacle containing an anticoagulant, or separated by continuous filtration or centrifugation of anticoagulated blood in an apheresis procedure.

Plasma, frozen: a plasma separated more than 8 h after collection of the blood and stored below -20 °C.

Plasma, fresh-frozen: a plasma separated within 8 h of donation, frozen rapidly and stored below -20 °C (and preferably below -30 °C).

Plasma, platelet-rich: a plasma containing at least 70% of the platelets of the original whole blood.

Plasma, freeze-dried: any one of the above forms of plasma that has been freeze-dried for preservation.

Plasma, recovered: plasma recovered from a whole blood donation.

Cryoprecipitated factor VIII: a crude preparation containing factor VIII that is obtained from single units (or small pools) of plasma derived either from whole blood or by plasmapheresis, by means of a process involving freezing, thawing and precipitation.

Serum: the liquid part of coagulated blood or plasma.

Red cells: whole blood from which most of the plasma has been removed and having an erythrocyte volume fraction greater than 0.7.

Red cells suspended in additive solution: red cells to which a preservative solution, for example containing adenine, glucose and mannitol, is added to permit storage for longer periods; the resulting suspension has an erythrocyte volume fraction of approximately 0.6-0.7.

Red cells, washed: red cells from which most of the plasma has been removed by one or more stages of washing with an isotonic solution.

Red cells, leukocyte-depleted: a unit of a red-cell preparation containing fewer than 1.2×10^9 leukocytes.

Red cells, leukocyte-poor: a unit of a red-cell preparation containing fewer than 5×10^6 leukocytes.

Red cells, frozen: red cells that have been stored continuously at −65 °C or below, and to which a cryoprotective agent such as glycerol has been added before freezing.

Red cells, deglycerolized: frozen red cells that have been thawed and from which glycerol has been removed by washing.

Platelets: platelets obtained either by separation of whole blood, buffy coat or platelet-rich plasma or by apheresis and suspended in a small volume of plasma from the same donation.

Leukocytes: leukocytes obtained either by the separation of whole blood or by apheresis and suspended in a small volume of plasma from the same donation.

Large-pool products

Bulk material: plasma, powder, paste or liquid material prepared by the fractionation of pooled plasma.

Final bulk: a sterile solution prepared from bulk material and bearing the corresponding batch number. It is used to fill the final containers.

> In some countries, the final bulk is distributed into containers through a sterilizing filter. If the total final bulk is not distributed into containers in one session, each of the filling lots is given a sub-batch number.

Filling lot (final lot): a collection of sealed final containers that are homogeneous with respect to composition and the risk of contamination during filling and (where appropriate) drying or other further processing such as heat treatment. A filling lot must therefore have been filled and (where appropriate) dried in one working session.

Part A. Requirements for the collection of source materials

1. Premises

The premises shall be of suitable size, construction and location to facilitate their proper operation, cleaning and maintenance in accordance with accepted rules of hygiene. They shall comply with the requirements of Good Manufacturing Practices for Pharmaceutical (*7*) and Biological (*8*) Products and in addition provide adequate space, lighting and ventilation for the following activities where applicable:

- The medical examination of individuals in private to determine their fitness as donors of blood and/or blood components and to provide an opportunity for the confidential self-exclusion of unsuitable potential donors.
- The withdrawal of blood from donors and, where applicable, the re-infusion of blood components with minimum risk of contamination and errors.
- The care of donors, including the treatment of those who suffer adverse reactions.
- The storage of whole blood and blood components in quarantine pending completion of processing and testing.
- The laboratory testing of blood and blood components.
- The processing and distribution of whole blood and blood components in a manner that prevents contamination and loss of potency.
- The performance of all steps in apheresis procedures, if applicable.
- The performance of labelling, packaging and other finishing operations in a manner that prevents errors.
- The storage of equipment.
- The separate storage of quarantined and finished products.
- The documentation, recording and storage of data on the donor, the donated blood and the ultimate recipient.

Mobile teams can be used for the collection of blood. Although the premises used by such teams may not comply with the more stringent requirements for centres built specially for the purpose, they must be adequate to ensure the safety of the donor, the collected blood or blood components and the staff participating in blood collection. The safety of the subsequent users of the premises should also not be forgotten.

2. Equipment

The equipment used in the collection, processing, storage and distribution of blood and blood components shall be calibrated, tested and validated before initial use, and shall be kept clean and maintained and checked regularly. The requirements of Good Manufacturing Practices for Pharmaceutical (*7*) and Biological (*8*) Products shall apply in every particular.

The equipment employed to sterilize materials used in the collection of blood or blood components or for the disposal of contaminated products shall ensure that contaminating microorganisms are destroyed and shall be validated for this purpose. The effectiveness of the sterilization procedure shall be not less than that achieved by a temperature of 121.5 °C maintained for 20 min by means of saturated steam at a pressure of 103 kPa (1.05 kgf/cm^2 or 15 lbf/in^2) or by a temperature of 170 °C maintained for 2 h with dry heat.

All contaminated material should be made safe before disposal. Disposal should comply with the relevant local laws.

Tests for sterility are given in the revised Requirements for Biological Substances No. 6 (General Requirements for the Sterility of Biological Substances) (9, pp. 40–61).

3. Personnel

An organization for the collection of blood or blood components shall be under the direction of a designated and appropriately qualified person who shall be responsible for ensuring that all operations are carried out properly and competently. The director shall have adequate knowledge and experience of the scientific and medical principles involved in the procurement of blood and, if applicable, the separation of blood components and the collection of such components by apheresis.

The director shall be responsible for ensuring that employees are adequately trained and acquire practical experience and that they are aware of the application of accepted good practice to their respective functions.

The director should have the authority to enforce or to delegate the enforcement of discipline among relevant employees.

The persons responsible for the collection of the blood and blood components shall be supervised by licensed physicians who shall be responsible for all medical decisions, for review of the procedures manual and for the quality-control programme, including techniques, equipment, procedures and staff.

The personnel responsible for the processing, storage, distribution and quality control of blood, blood components and plasma shall be adequate in number and each member of the personnel shall have a suitable educational background and training or experience that will ensure competent performance of assigned functions so that the final product has the required safety, purity, potency and efficacy.

4. Donors

4.1 *Donor selection*

The provision of blood, blood components and plasma derivatives from voluntary, non-remunerated donors should be the aim of all countries.

In selecting individuals for blood donation, it is most important to determine whether the person is in good health, in order to protect the donor against damage to his or her own health and to protect the recipient against exposure to diseases or to medicinal products from the blood or blood products. It should be recognized that the donor selection process contributes significantly to the safety of blood products derived from large plasma pools. The following provisions apply to donations of blood or blood components not intended for autologous use.

The health of a donor shall be determined by a licensed physician or a person under the direct supervision of a licensed physician, and the donor shall be free from any disease transmissible by blood transfusion in so far as can be determined by history-taking and examination (see section 4.3). Donors shall be healthy persons of either sex between the ages of 18 and 65 years.

> In some countries, there is no upper limit to the age of the donor. With parental consent the minimum age may be lowered to 16 years.
>
> Red blood cells from donors with glucose-6-phosphate dehydrogenase deficiency, sickle-cell trait or other inherited erythrocyte abnormalities may give rise to transfusion reactions under certain circumstances. Decisions regarding the suitability of such donors should be made by the national control authority.

A donor should be considered for plasmapheresis only where the procedures involved result in products or services shown to serve accepted medical purposes, including prophylaxis, therapy and diagnosis, as verified by valid scientific evidence. All donors should be certified as acceptable, at the time of each plasmapheresis procedure, by a registered physician or by trained personnel under the direct supervision of the physician.

Those eligible for apheresis donation include: (a) healthy persons who fulfil the general criteria for blood donors; (b) persons with antibody levels that have been increased, either naturally or by immunization; (c) subject to (a) above, persons with plasma that is of value for diagnostic or reference purposes; and (d) persons whose blood may be used in the preparation of certain vaccines.

> When a potential donor does not fulfil the general criteria for blood donation, the acceptance of her or him as a donor for a specific component of blood *should be at the discretion of the responsible physician. Where appropriate,* the physician should have access to an ethical committee.

Donor education and selection programmes are intended to prevent potentially infectious units of blood and plasma from being collected. It is essential that such programmes are comprehensible and readily accessible to all potential donors.

To reduce the likelihood of transmitting infections, all potential donors should be informed of factors in their history or behaviour that may increase their risk of being infected. The national control authority must determine the appropriate exclusion criteria for the country concerned.

Persons in the following categories shall be excluded from acting as donors:

- those with clinical or laboratory evidence of infectious disease, e.g. infection with hepatitis viruses, HIV-1 or HIV-2;
- past or present intravenous drug abusers;
- men who have had a sexual relationship with another man;

- men and women who have engaged in prostitution;
- those with haemophilia or other clotting-factor defects who have received clotting-factor preparations;
- sexual partners of any of the above.

In some countries, the sexual partners of those at risk of transmitting infections are excluded from acting as donors for only one year.

Persons who have received blood transfusions should be excluded from acting as donors for at least one year.

Donors should be made aware before donating blood that it will be tested for the presence of serological markers of infection. It is advisable that the right to test donations and the legal implications of testing donations should be clarified by the appropriate authority.

4.2 *Donation frequency and volume*

4.2.1 *Whole blood*

The frequency of whole-blood donations shall not exceed once every two months, with a maximum volume in any consecutive 12-month period of 3 l.

A standard donation should not be collected from persons weighing less than 50 kg.

A *standard donation* is 450 ml; an optimum blood/anticoagulant ratio is 7 to 1.

The frequency of donation may have to be modified on an individual basis. In general, premenopausal women should not donate blood as frequently as men.

4.2.2 *Plasma*

Plasma donors can be divided into three groups: those who donate at a frequency comparable to that allowed for whole-blood donations; those who donate two to three times as frequently as whole-blood donors; and those who donate at a maximum of twice a week. The first group shall be accepted on the basis of the general criteria for blood donors.

The maximum volume of plasma that may be removed from a donor during one plasmapheresis procedure shall be determined by the national health authority, and shall depend on whether the plasma is obtained by manual or automated plasmapheresis.

In some countries, the volume of plasma collected during a manual procedure is the quantity obtained from 1.0–1.2 l of whole blood. The volume of plasma collected during an automated procedure depends on the equipment used.

It is difficult to specify the maximum volumes of plasma that can be safely collected from donors until more definitive data are available on the effects of plasmapheresis on donors. The limits imposed in different countries vary, and depend on the nutritional status of the donor.

If a plasma donor donates a unit of whole blood or if the red blood cells are