HUMAN PLASMA FOR FRACTIONATION

Plasma humanum ad separationem

DEFINITION
Human plasma for fractionation is the liquid part of human blood 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; it is intended for the manufacture of plasma-derived products.

PRODUCTION

DONORS

Only a carefully selected, healthy donor who, as far as can be ascertained after medical examination, laboratory blood tests and a study of the donor’s medical history, is free from detectable agents of infection transmissible by plasma-derived products may be used. Recommendations in this field are made by the Council of Europe [Recommendation No. R (95) 15 on the preparation, use and quality assurance of blood components, or subsequent revision] and the European Union [Council Recommendation of 29 June 1998 on the suitability of blood and plasma donors and the screening of donated blood in the European Community (98/463/EC)].

Immunisation of donors. Immunisation of donors to obtain immunoglobulins with specified activities may be carried out when sufficient supplies of material of suitable quality cannot be obtained from naturally immunised donors. Recommendations for such immunisation are formulated by the World Health Organisation (Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives, WHO Technical Report Series, No. 840, 1994 or subsequent revision).

Records. Records of donors and donations made are kept in such a way that, while maintaining the required degree of confidentiality concerning the donor’s identity, the origin of each donation in a plasma pool and the results of the corresponding acceptance procedures and laboratory tests can be traced.

Laboratory tests. Laboratory tests are carried out for each donation to detect the following viral markers:

1. antibodies against human immunodeficiency virus 1 (anti-HIV-1),
2. antibodies against human immunodeficiency virus 2 (anti-HIV-2),
3. hepatitis B surface antigen (HBsAg),
4. antibodies against hepatitis C virus (anti-HCV).

Pending complete harmonisation of the laboratory tests to be carried out, the competent authority may require that a test for alanine aminotransferase (ALT) also be carried out. The test methods used are of suitable sensitivity and specificity and comply with the regulations in force. If a repeat-reactive result is found in any of these tests, the donation is not accepted.

INDIVIDUAL PLASMA UNITS

The plasma is prepared by a method that removes cells and cell debris as completely as possible. Whether prepared from whole blood or by plasmapheresis, the plasma is separated from the cells by a method designed to prevent the introduction of micro-organisms. No antibacterial or antifungal agent is added to the plasma. The containers comply with the requirements for glass containers (3.2.1) or for plastic containers for blood and blood components (3.2.2). The containers are closed so as to prevent contamination.

When obtained by plasmapheresis, plasma intended for the recovery of proteins that are labile in plasma is frozen by cooling rapidly at −30 °C or below as soon as possible and at the latest within 24 h of collection.

When obtained from whole blood, plasma intended for the recovery of proteins that are labile in plasma is separated from cellular elements and is frozen by cooling rapidly at −30 °C or below as soon as possible and at the latest within 24 h of collection.

When obtained from whole blood, plasma intended solely for the recovery of proteins that are not labile in plasma is separated from cellular elements and frozen at −20 °C or below as soon as possible and at the latest within 72 h of collection.

It is not intended that the determination of total protein and factor VIII shown below be carried out on each unit of plasma. They are rather given as guidelines for good manufacturing practice, the test for factor VIII being relevant for plasma intended for use in the preparation of concentrates of labile proteins.

The total protein content of a unit of plasma depends on the serum protein content of the donor and the degree of dilution inherent in the donation procedure. When plasma is obtained from a suitable donor and using the intended proportion of anticoagulant solution, a total protein content complying with the limit of 50 g/l is obtained. If a volume of blood or plasma smaller than intended is collected into the anticoagulant solution, the resulting plasma is not necessarily unsuitable for pooling for fractionation. The aim of good manufacturing practice must be to achieve the prescribed limit for all normal donations.

Preservation of factor VIII in the donation depends on the collection procedure and the subsequent handling of the blood and plasma. With good practice, 0.7 IU/ml can usually be achieved, but units of plasma with a lower activity may still be suitable for use in the production of coagulation factor concentrates. The aim of good manufacturing practice is to conserve labile proteins as much as possible.

Total protein. Carry out the test using a pool of not fewer than 10 units. Dilute the pool with a 9 g/l solution of sodium chloride R to obtain a solution containing about 15 mg of protein in 2 ml. To 2.0 ml of this solution in a round-bottomed centrifuge tube add 2 ml of a 75 g/l solution of sodium molybdate R and 2 ml of a mixture of 1 volume of nitrogen-free sulphuric acid R and 30 volumes of water R. Shake, centrifuge for 5 min, decant the supernatant liquid and allow the inverted tube to drain on filter paper. Determine the nitrogen in the residue by the method of sulphuric acid digestion (2.5.9) and calculate the protein content by multiplying the quantity of nitrogen by 6.25. The total protein content is not less than 50 g/l.

Factor VIII. Carry out the test using a pool of not fewer than 10 units. Thaw the samples to be examined, if necessary, at 37 °C. Carry out the assay of factor VIII (2.7.4), using a reference plasma calibrated against the International Standard for blood coagulation factor VIII in plasma. The activity is not less than 0.7 IU/ml.
POOLED PLASMA

During the manufacture of plasma products, the first homogeneous pool of plasma (for example, after removal of cryoprecipitate) is tested for HBsAg, for hepatitis C virus antibodies and for HIV antibodies using test methods of suitable sensitivity and specificity; the pool must give negative results in these tests.

The plasma pool is also tested for hepatitis C virus RNA using a validated nucleic acid amplification technique (2.6.21). A positive control with 100 IU/ml of hepatitis C virus RNA and, to test for inhibitors, an internal control prepared by addition of a suitable marker to a sample of the plasma pool are included in the test. The test is invalid if the positive control is non-reactive or if the result obtained with the internal control indicates the presence of inhibitors. The plasma pool complies with the test if it is found non-reactive for hepatitis C virus RNA.

Hepatitis C virus RNA for NAT testing BRP is suitable for use as a positive control.

CHARACTERS

Before freezing, a clear to slightly turbid liquid without visible signs of haemolysis; it may vary in colour from light yellow to green.

STORAGE

Store and transport frozen plasma at or below −20 °C; the plasma may still be used for fractionation if the temperature is between −20 °C and −15 °C for not more than a total of 72 h without exceeding −15 °C on more than one occasion as long as the temperature is at all times −5 °C or lower.

LABELLING

The label enables each individual unit to be traced to a specific donor.

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HUMAN PLASMA (POOLED AND TREATED FOR VIRUS INACTIVATION)

Plasma humanum collectum deinde conditum ad viros exstinguendos

DEFINITION

Human plasma pooled and treated for virus inactivation is a frozen or freeze-dried, sterile, non-pyrogenic preparation obtained from human plasma derived from donors belonging to the same ABO blood group. The preparation is thawed or reconstituted before use to give a solution for infusion. The human plasma used complies with the monograph on Human plasma for fractionation (0853).

PRODUCTION

The units of plasma to be used are cooled to −30 °C or lower within 6 h of separation of cells and in any case within 24 h of collection.

The pool is prepared by mixing units of plasma belonging to the same ABO blood group.

The pool of plasma is tested for hepatitis B surface antigen (HBsAg), for hepatitis C virus antibodies and for HIV antibodies using test methods of suitable sensitivity and specificity; the pool must give negative results in these tests. The plasma pool is also tested for hepatitis C virus RNA using a validated nucleic acid amplification technique (2.6.21).

A positive control with 100 IU of hepatitis C virus RNA per millilitre and, to test for inhibitors, an internal control prepared by addition of a suitable marker to a sample of the plasma pool are included in the test. The test is invalid if the positive control is non-reactive or if the result obtained with the internal control indicates the presence of inhibitors. The pool complies with the test if it is found non-reactive for hepatitis C virus RNA.

Hepatitis C virus RNA for NAT testing BRP is suitable for use as a positive control.

To limit the potential burden of B19 virus in plasma pools, the plasma pool is also tested for B19 virus using a validated nucleic acid amplification technique (2.6.21).

A positive control with 104 IU of B19 virus DNA per millilitre and, to test for inhibitors, an internal control prepared by addition of a suitable marker to a sample of the plasma pool are included in the test. The test is invalid if the positive control is non-reactive or if the result obtained with the internal control indicates the presence of inhibitors. The plasma pool contains not more than 104 IU of B19 virus DNA per millilitre.

B19 virus DNA for NAT testing BRP is suitable for use as a positive control.

The method of preparation is designed to minimise activation of any coagulation factor (to minimise potential thrombogenicity) and includes a step, or steps that have been shown to inactivate known agents of infection; if substances are used for the inactivation of viruses during production, the subsequent purification procedure must be validated to demonstrate that the concentration of these substances is reduced to a suitable level and that any residues are such as not to compromise the safety of the preparation for patients.

A typical method to inactivate enveloped viruses is the solvent-detergent process which uses treatment with a combination of tributyl phosphate and octoxinol 10; these reagents are subsequently removed by oil extraction or by solid phase extraction so that the amount in the final product is less than 2 µg/ml for tributyl phosphate and less than 5 µg/ml for octoxinol 10.

No antimicrobial preservative is added.

The solution is passed through a bacterioretentive filter, distributed aseptically into the final containers and immediately frozen; it may subsequently be freeze-dried.

Plastic containers comply with the requirements for sterile plastic containers for human blood and blood components (3.2.3).

Glass containers comply with the requirements for glass containers for pharmaceutical use (3.2.1).

CHARACTERS

The frozen preparation, after thawing, is a clear or slightly opalescent liquid free from solid and gelatinous particles.

The freeze-dried preparation is an almost white or slightly yellow powder or friable solid.

Thaw or reconstitute the preparation to be examined as stated on the label immediately before carrying out the identification, tests and assay.

IDENTIFICATION

A. Examine by electrophoresis (2.2.31) comparing with normal human plasma. The electropherograms show the same bands.

B. It complies with the test for anti-A and anti-B haemagglutinins (see Tests).

TESTS

pH (2.2.3): 6.5 to 7.6.