MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

PHARMACOPOEIA MONOGRAPH

Human plasma for fractionation	**PM.3.3.2.0001.15** Replaces the Pharmacopoeia
Monograph 42-0091-02	

The present Pharmacopoeia Monograph applies to plasma for fractionation, which is the liquid part of human blood remaining after separation of blood cellular elements, with an anticoagulant added. Plasma for fractionation is obtained from human whole blood by means of centrifugation, apheresis, etc. Human plasma for fractionation should contain no antibacterial or antifungal agents.

Human plasma for fractionation is used as a substance for manufacturing human blood preparations.

Donors. Human plasma may be produced from pooled plasma of healthy donors recruited by means of medical work-up, medical history analysis, and laboratory investigations of blood samples, in accordance with the requirements of active regulatory legal acts.

Registered data should enable identification and traceability of the donor and each plasma unit included in the pool, as well as of related samples obtained for laboratory investigations.

Individual plasma unit. An individual plasma unit is subject to obligatory testing for the absence of hepatitis B virus surface antigen, anti-hepatitis C virus antibodies, HIV p24 antigens, and antibodies to HIV-1 and HIV-2 viruses and to the syphilis pathogen. Plasma samples producing negative enzyme immunoassay results are united in mini-pools and investigated for the presence of nucleic acids of human immunodeficiency virus, hepatitis B and hepatitis C viruses. If the tests

produce positive results, plasma obtained from such donors should be discarded and disposed of.

Plasma designed for the isolation of labile proteins (blood coagulation factors) should be frozen to a temperature of minus 25 °C or lower within 24 hours after donation.

Plasma designed for the isolation of stable proteins (albumin, immunoglobulins) and obtained by means of apheresis should be frozen to a temperature of minus 20 °C or lower within 24 hours after donation, whereas plasma obtained by different methods has to be frozen to a temperature of minus 20 °C or lower within 72 hours after donation.

Disposable polymeric containers meeting applicable requirements should be used for the preparation of blood and blood components. The package should be air-tight, to rule out microbial contamination.

Quarantine. Individual plasma units are subject to quarantine in accordance with applicable regulatory legal acts. If a donor is diagnosed with a blood-borne infection during the quarantine period or found to have specific and non-specific markers of blood-borne infections in the blood after the end of the quarantine period, the frozen plasma obtained from this donor should be isolated, disinfected, and disposed of, and this procedure should be registered in all cases.

Prior to obtaining an industrial pool (load), individual plasma units are united to test them on the required parameters. When manufacturing blood preparations, the industrial plasma pool (load) should always be tested for the HIV p24 antigen, antibodies to HIV-1 and HIV-2 viruses, antibodies to the hepatitis C virus, the hepatitis B virus surface antigen, and the syphilis pathogen by enzyme immunoassay, as well as for the presence of nucleic acids of human immunodeficiency virus and hepatitis B and hepatitis C viruses, by means of the polymerase chain reaction.

The industrial pool should produce negative results when tested in the plasma viral safety tests.

The amount of pooled plasma units should be specified in the Pharmacopoeia Monograph.

TESTS

Description. In the frozen state: a yellow dense solidified cake. Before freezing and after defreezing (thawing): a light yellow to greenish, transparent or slightly opalescent liquid. No feculence or flocculi may be present.

Note

Thawing of individual plasma units should be carried out at (35 - 37) °C for 15 minutes.

Identification (species specificity). Identity of plasma for fractionation is confirmed by the presence of only human serum proteins. The test is carried out using sera against human, bovine, horse, and porcine serum proteins, with the gel immunoelectrophoresis method, as described in the General Pharmacopoeia Monograph "Agarose gel immunoelectrophoresis", or with the gel immunodiffusion method, as specified in the General Pharmacopoeia Monograph "Gel immunodiffusion".

Blood pigments. The optical density of the tested solution should be not more than 0.25. The test is carried out in accordance with the General Pharmacopoeia Monograph "Spectrophotometry in the ultraviolet and visible regions", using cuvettes with an optical path length of 10 mm, at wavelength 403 nm, versus water.

Note

Preparation of the tested sample. The tested sample of plasma for fractionation is diluted with 0.9 % sodium chloride solution in the 1:4 ratio.

pH value. From 6.5 to 7.5. The test is carried out by potentiometry, in accordance with the General Pharmacopoeia Monograph "Ionometry", using thawed plasma.

Sterility. The medicinal product is required to be sterile. The test is carried out in accordance with the General Pharmacopoeia Monograph "Sterility". The test method used should be specified in the Pharmacopoeia Monograph.

Protein content. Not less than 5 %. The test is carried out by an appropriate test method, in accordance with the General Pharmacopoeia Monograph "Determination of protein".

Specific activity. The quantities of antibacterial antibodies (against at least one pathogen) and antiviral antibodies (against at least one pathogen) should be specified for human plasma for fractionation used in the manufacture of normal human immunoglobulin preparations; for instance, the content of anti-alpha-staphylolysin should be not less than 0.5 IU/mL and the content of anti-measles antibodies should be not less than 1:80. The test is carried out in accordance with the method(s) specified in the Normative Document (for instance, anti-measles antibody content is determined by the passive haemagglutination assay, and anti-alpha-staphylolysin content is found in the reaction neutralizing the haemolytic properties of staphylococcal alpha-toxin), using appropriate standard samples.

The quantity of specific antibodies should be specified for human plasma for fractionation used in the manufacture of specific and non-specific human immunoglobulin preparations. For instance, plasma for fractionation used in the manufacture of human antistaphylococcal immunoglobulin should have an anti-alpha-staphylolysin content not less than 3 IU/mL; plasma for fractionation used in the manufacture of human immunoglobulin against tick-borne encephalitis should have a tick-borne encephalitis virus antibody content not less than 1:10; plasma for fractionation used in the manufacture of human immunoglobulin against hepatitis B should have a hepatitis B virus surface antigen (HBsAg) content not less than 5 IU/mL, and so on. The test is carried out in accordance with the method(s) specified in the Normative Document, using appropriate standard samples.

Plasma for fractionation used in the manufacture of blood coagulation factor preparations should be tested for Factor VIII activity in accordance with the General Pharmacopoeia Monograph "Determination of blood coagulation factor activity". Factor VIII activity should be not less than 0.7 IU/mL. The test is carried out on a pooled sample containing not less than 10 individual plasma units.

Viral safety

Hepatitis B virus surface antigen (HBsAg) and nucleic acid. The medicinal product should contain no hepatitis B virus surface antigen or nucleic acid. The test is carried out by enzyme immunoassay and the polymerase chain reaction, using commercial test systems approved for use in the Russian Federation and in accordance with the accompanying Instructions for Use.

Anti-human immunodeficiency virus (HIV-1 and HIV-2) antibodies and human immunodeficiency virus nucleic acid. The medicinal product should contain no anti-human immunodeficiency virus (HIV-1 and HIV-2) antibodies and no human immunodeficiency virus nucleic acid. The test is carried out by enzyme immunoassay and the polymerase chain reaction, using commercial test systems approved for use in the Russian Federation and in accordance with the accompanying Instructions for Use.

Anti-hepatitis C virus antibodies and hepatitis C virus nucleic acid. The medicinal product should contain no anti-hepatitis C virus antibodies and no hepatitis C virus nucleic acid. The test is carried out by enzyme immunoassay and the polymerase chain reaction, using commercial test systems approved for use in the Russian Federation and in accordance with the accompanying Instructions for Use.

Anti-syphilis pathogen antibodies. Plasma should contain no anti-syphilis pathogen antibodies. The test is carried out by the immunological method, in the microprecipitation reaction with commercial diagnostic kits, or by enzyme immunoassay using commercial test systems approved for use in the Russian Federation and in accordance with the accompanying Instructions for Use.

Packaging and Labeling. The primary package (disposable polymeric containers) should be air-tight, ensure preservation of claimed plasma properties throughout the approved shelf-life, and be approved for use in the packaging of medicinal products.

The package label should include the name and address of the donation organization providing blood and blood components, the identification number of the donation, the ABO blood group and the Rhesus factor group, the date of donation, the date of manufacture of the plasma unit (if not coinciding with the date of donation), the expiry date, the name and volume of the anticoagulant and / or accessorial solution, the name of the blood component, the volume or weight of the blood or blood component, the storage conditions, mentioning of any additional processing (irradiation, filtration, inactivation), and the inscription: «Contains no antibodies to HIV-1, HIV-2, hepatitis C virus and no hepatitis B virus surface antigen».

Storage. The medicinal product should be stored at a temperature of minus 30 °C or lower.

Transportation. Transportation should be done at a temperature of minus 25 ^{o}C or lower, using special refrigerators (chambers, modules) equipped with sensors and temperature-monitoring appliances.