MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

GENERAL PHARMACOPOEIA MONOGRAPH

Human immunoglobulins	**GPM**.1.8.1.0003.15 First Edition

The present General Pharmacopoeia Monograph applies to a group of immunobiological preparations, human immunoglobulins. Human immunoglobulins are the immunologically active protein fraction of human serum or plasma carrying antibody activity of varying specificity. Immunoglobulin preparations are either a liquid or a powder (hygroscopic cake) containing immunoglobulins, predominantly of the G class (Ig G) – antibodies against various pathogens of bacterial and / or viral infections and / or their toxins.

The raw material in the manufacture of human immunoglobulins is plasma obtained from healthy donors and corresponding to the requirements of the "Plasma for fractionation" Pharmacopoeia Monograph.

There are following types of human immunoglobulins:

– normal immunoglobulins (for intramuscular, subcutaneous, intravenous administration and for oral administration) that are used for specific prevention of bacterial and viral infections, to boost non-specific resistance, as well as for the treatment of infectious-toxic and viral diseases;

– specific immunoglobulins employed for the prevention and / or treatment of a certain infection;

– immunoglobulins for special uses (for the treatment of allergic diseases etc.).

Human immunoglobulins are at least 95 % Class G immunoglobulins.

Human immunoglobulins contain no preservatives and no antibiotics.

MANUFACTURE

Human immunoglobulins are produced from pooled plasma obtained from at least 1000 healthy donors (for specific immunoglobulins, the number of donors is not limited), using methods with demonstrated immunoglobulin fraction isolation efficacy and proven viral and specific safety.

The manufacture of human immunoglobulins should guarantee preservation of the structure and function of immunoglobulin proteins responsible for the specific and viral safety of the medicinal product, precluding contamination with foreign agents, and including a manufacturing stage (or stages) ensuring inactivation and elimination of infectious agents. Antibacterial and antiviral efficacy of medicinal products should be guaranteed by appropriate antibody concentration achieved in the manufacturing process (not less than three-fold for medicinal products with a protein concentration of 4.5 % to 5.5 % and not less than six-fold for medicinal products with a protein concentration of 9.0 % to 16.0 %).

TESTS

Description. For liquid products: a colourless or light yellow, transparent or slightly opalescent solution; for lyophilized products: a white or light yellow powder or amorphous hygroscopic cake (unless different requirements are included in the Pharmacopoeia Monograph or in the Normative Document).

Identification. Identity is confirmed by the presence of only human serum proteins. The test is carried out by gel immunoelectrophoresis, using sera against human, bovine, horse, and porcine serum proteins, as described in the General Pharmacopoeia Monograph “Agarose gel immunoelectrophoresis”. This test may also be performed with the gel immunodiffusion method. The test method should be specified in the Pharmacopoeia Monograph or in the Normative Document. The test should produce precipitation lines only with the serum against human serum proteins.

Dissolution time (for lyophilized medicinal products). Not more than 20 minutes, unless otherwise specified in the Pharmacopoeia Monograph or in the Normative Document. A description of the method should be included, along with the solvent used, its volume, and the dissolution conditions (solvent temperature, need for mixing, etc.).

Transparency. A transparent or slightly opalescent solution, unless otherwise specified in the Normative Document. The test is carried out in accordance with the General Pharmacopoeia Monograph "Transparency and turbidity of liquids". Another acceptable option is spectrophotometric determination of the optical density of the solution in accordance with the General Pharmacopoeia Monograph "Spectrophotometry in the ultraviolet and visible regions". The test method should be specified in the Normative Document.

Colour intensity. A colourless or light yellow solution, unless otherwise specified in the Pharmacopoeia Monograph or in the Normative Document. The test is carried out in accordance with the General Pharmacopoeia Monograph "Colour intensity of liquids". Another acceptable option is spectrophotometric determination of the optical density of the solution in accordance with the General Pharmacopoeia Monograph "Spectrophotometry in the ultraviolet and visible regions".

The "Colour intensity" or "Colour intensity of reconstituted solution" section should include requirements established for the colour intensity of the medicinal product or solution obtained with the solvent specified in the Instructions for Use, as well as the methods used for testing and data interpretation.

Weight loss on drying (for lyophilized medicinal products)**.** Not more than 3 %. The test is carried out by gravimetry, in accordance with the General Pharmacopoeia Monograph "Weight loss on drying" or by other validated methods specified in the Pharmacopoeia Monograph or in the Normative Document.

Particulate matter. Visible particulate matter should be absent. The test is carried out in accordance with the General Pharmacopoeia Monograph "Visible

particulate matter in medicinal products for parenteral use and ophthalmic dosage forms".

pH value. Normative requirements should be included in the Normative Document. Before the test, the medicinal product is diluted to a 1 % concentration with 0.9 % sodium chloride solution (pH value 7.0 – 7.2). The test is carried out by potentiometry in accordance with the General Pharmacopoeia Monograph "Ionometry". For dry pharmaceutical forms, the name of the solvent should be specified, the reconstitution technique described, and normative requirements established for the reconstituted medicinal product included.

Protein content. Normative requirements should be included in the Normative Document. The test is carried out by colourimetry with the Biuret reagent in accordance with the General Pharmacopoeia Monograph "Determination of protein".

Electrophoretic homogeneity. The main IgG immunoglobulin fraction should constitute not less than 95 % of the total protein content. The test is carried out in accordance with the General Pharmacopoeia Monograph "Homogeneity testing for medicinal products containing human or animal serum by cellulose acetate electrophoresis".

Molecular parameters. Normative requirements should be included in the Normative Document. The test is carried out in accordance with the General Pharmacopoeia Monograph "HPLC determination of immunoglobulin molecular parameters".

Fractional composition. An intensive IgG precipitation line should be observed, and there should be not more than four additional lines. The test is carried out by gel immunoelectrophoresis, using a serum against human serum proteins in accordance with the General Pharmacopoeia Monograph "Agarose gel immunoelectrophoresis".

Heat stability (for liquid pharmaceutical forms). The medicinal product should remain liquid and form no gel after being exposed to a temperature of (56±1) °C for 4 hours in a water bath or water thermostat.

Sterility. The medicinal product is required to be sterile. The test is carried out in accordance with the General Pharmacopoeia Monograph “Sterility”.

Pyrogenicity or Bacterial endotoxins (for parenteral pharmaceutical forms)**.** The medicinal product is required to be non-pyrogenic or its content of bacterial endotoxins should lie within established limits. The test is carried out in accordance with the General Pharmacopoeia Monograph “Pyrogenicity” or the General Pharmacopoeia Monograph “Bacterial endotoxins”.

Abnormal toxicity. The medicinal product is required to be non-toxic. The test is carried out in accordance with the General Pharmacopoeia Monograph “Abnormal toxicity”.

Antibody content (specific activity). The Normative Document should specify the quantity of antibacterial antibodies (against at least one pathogen) and / or antiviral antibodies (against at least one pathogen). The test is carried out in accordance with the method specified in the Pharmacopoeia Monograph, using appropriate standard samples.

Hepatitis B virus surface antigen (HBsAg). The medicinal product should contain no hepatitis B virus surface antigen. The test is carried out by enzyme immunoassay, using test systems approved for use and having a sensitivity not less than 0.1 IU/mL according to the Instructions for Use.

Anti-hepatitis C virus antibodies. The medicinal product should contain no anti-hepatitis C virus antibodies. The test is carried out by enzyme immunoassay, using test systems approved for use and having 100 % sensitivity and specificity according to the Instructions for Use.

Anti-human immunodeficiency virus (HIV-1 and HIV-2) antibodies and HIV-1 p24 antigen. The medicinal product should contain no anti-human immunodeficiency virus (HIV-1 and HIV-2) antibodies and no HIV-1 p24 antigen. The test is carried out by enzyme immunoassay, using test systems approved for use and having 100 % sensitivity and specificity according to the Instructions for Use.

Packaging and Labeling. In accordance with the General Pharmacopoeia Monograph “Medicinal products containing human plasma”.

The secondary (consumer) package of the medicinal product should contain the following 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 away from light, in the temperature range of 2 to 8 °C, unless otherwise specified in the Pharmacopoeia Monograph or in the Normative Document.