MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

GENERAL PHARMACOPOEIA MONOGRAPH

Immunoglobulins and sera (antibodies), heterologous	**GPM**.1.8.1.0004.15 First Edition

The present General Pharmacopoeia Monograph applies to heterologous immunoglobulins and sera (antibodies) (referred to herein under as sera), which are medicinal products that contain purified immunoglobulins or their fragments obtained from serum or plasma of animals of various species following immunization with respective antigens. Sera contain specific antibodies that neutralize or bind the antigens that were administered to immunize the animals. Antigens may include microbial or other toxins, bacteria, viruses, and venoms (of snakes, spiders, scorpions), as well as some human tissues.

Sera may contain antibodies to one (monovalent sera) or several (polyvalent sera) antigens. Polyvalent sera are obtained by immunization of animals with several types of antigens or pooling a few monovalent sera. Sera are supplied as liquid or lyophilized medicinal products designed for intramuscular, subcutaneous, intravenous administration, as well as for administration into the neural canal.

MANUFACTURE

Requirements established for serum producing animals

Animals used in the manufacture of sera should be absolutely healthy and free from the helminths and infectious agents specified in the approved list of diseases, including pathogens of diseases specific for the animal breeding area.

Cattle from regions known to be contaminated with spongiform encephalopathy should not be used as serum producers.

Animals that have been administered antibiotics may be used in the manufacture of sera only after the time required for complete elimination of the antibiotic from the body. Penicillin antibiotics should not be administered to treat serum producing animals.

Serum producing animals should be quarantined after they are received, and horses and cattle should additionally undergo vaccination with tetanus toxoid.

Immunization of animals

After the animals are immunized, the antigen may be administered with the adjuvant. The health status of the animals should be constantly monitored and the production of specific antibodies regularly assessed during the immunization cycles. If the animals develop abnormalities not characteristic of the antigen being used, use of all animals in the respective group should be suspended until these abnormalities have been shown not to affect the safety and efficacy of the end product. When immunizing serum producing animals with live microorganisms, a time sufficient for the elimination of the microorganisms used should be allowed between the last immunization and blood-letting.

Collection of blood or plasma

Collection of blood or plasma is done by venipuncture or plasmapheresis, using aseptic technique. The blood / plasma collection area should be isolated from the animals housing place. Plasmas obtained from different animals may be pooled. Obtained plasma must be sterile.

Obtaining immunoglobulins or immunoglobulin fragments

Immunoglobulins or immunoglobulin fragments are obtained by salt fractionation and enzymatic processing, using different methods for the elimination of ballast proteins and impurities (chromatography, membrane filtration, fermentation, and other appropriate chemical and physical methods) that should ensure that the obtained product is free from contamination and serum protein aggregates and fragments that can affect its safety and quality. The technological

process used to obtain immunoglobulins or immunoglobulin fragments must be validated. For products containing immunoglobulin fragments, the methods that demonstrate the correctness of established normative requirements should be specified to guarantee that the fragmentation procedure is performed as required.

TESTS

Description. For liquid products: a colourless or yellowish, transparent or slightly opalescent solution; for lyophilized products: a white or light yellow powder or amorphous, hygroscopic cake.

Identification. Identity is confirmed by immunological methods (immune electrophoresis, gel immunodiffusion method, etc.). The activity quantification method may be used for identification.

Transparency. A transparent or slightly opalescence solution, unless otherwise specified in the Pharmacopoeia Monograph or in the Normative Document. The test method should be specified. The test is carried out in accordance with the General Pharmacopoeia Monograph “Transparency and turbidity of liquids”.

Colour intensity. A colourless or yellowish solution. The test is carried out in accordance with the General Pharmacopoeia Monograph “Colour intensity of liquids”.

Weight loss on drying. Not more than 3 % for lyophilized medicinal products. The test is carried out by gravimetry, in accordance with the General Pharmacopoeia Monograph “Weight loss on drying”.

Dissolution time. Not more than 20 minutes for lyophilized medicinal products. The test method should be specified in the Normative Document.

pH value. From 5.0 to 7.2. The test is carried out by potentiometry in accordance with the General Pharmacopoeia Monograph “Ionometry”.

Extractable volume. The extractable volume should be not less than the nominal value. The test is carried out in accordance with the General Pharmacopoeia Monograph “Extractable volume for parenteral pharmaceutical forms”.

Osmolality. Not more than 240 mOsmol/kg. The test is carried out in accordance with the General Pharmacopoeia Monograph “Osmolarity” for medicinal products designed for intravenous administration, specifying the solvent and its volume.

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”.

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

Pyrogenicity. The medicinal product is required to be non-pyrogenic. The test is carried out in accordance with the General Pharmacopoeia Monograph “Pyrogenicity”. The test dose used and acceptable temperature change limits should be specified. One millilitre of the medicinal product per kilogramme of rabbit body weight is administered. For lyophilized medicinal products, the solvent and its volume should be specified.

Bacterial endotoxins. The normative requirements and the requirements established for the sample preparation procedure and the test dose (in weight, volume, or other units) should be specified in the Normative Document. The test is carried out in accordance with 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”. The test doses, method of administration, and observation time should be specified.

Specific activity. The established specific activity requirements should be specified and the specific activity quantification method used described. Specific activity of liquid medicinal products is expressed as the antibody content per unit of volume. For lyophilized medicinal products, the activity of the contents of the primary package or the activity per unit of volume obtained after dissolution in a

certain amount of the solvent should be specified. Antibody levels are expressed in International Units (IU). The method description should include the requirements established for experimental animals (species, line, weight, gender, amount); a description of the dosing regimen and method of administration of the medicinal product, mention of any use of standard samples (if necessary), the doses used; requirements established for reagents, test toxins, and viruses, as well as their doses; observation times and parameters assessed, calculation methods and statistical analyses used (if necessary).

If specific activity is determined *in vitro*, a description of the method used, the requirements established for reagents, and parameters evaluated should be included.

Activity per protein content unit (if required). The requirements should be described in the Pharmacopoeia Monograph or in the Normative Document. This type of activity is expressed as the number of activity units (for instance, IU) per an established protein content. The parameter is calculated by dividing the activity per volume unit by the amount of protein found in the same volume.

Substances added to the medicinal product. If the medicinal product contains preservatives, stabilizers, or fillers, their acceptable amount per volume unit (for liquid medicinal products) or the primary package contents (for lyophilized medicinal products), as well as the test methods used, should be specified. The amount of a preservative should not be less than the established effective minimum and should not exceed the label claim by more than 15 %.

Stability. The amount of a stabilizer should be not less than 80 % and not more than 120 % of the label claim. The stabilizer content is determined by means of an appropriate physicochemical method.

Solvents and reagents supplied with the medicinal product. A specific serum should be supplied along with a serum of the respective animal species diluted 1:100 and designed for intradermal testing of a patient’s sensitivity to the medicinal product, if required by the Prescribing Information.

Solvents supplied with lyophilized medicinal products should be solvents approved for medical use through the respective route of administration, which have no effect on quality of the medicinal product. The solvent quality requirements should be included in the manufacturer's Normative Document, which should specify all quality parameters required for the control of the solvent.

Packaging and Labeling. In accordance with the General Pharmacopoeia Monograph "Immunobiological medicinal products".

Transportation and Storage. The medicinal product should be stored away from light, in the temperature range of 2 to 8 °C. Liquid medicinal products must not be frozen.