

MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

GENERAL PHARMACOPOEIA MONOGRAPH

Pharmaceutical forms

GPM.1.4.1.0007.15

for parenteral administration

Replaces the State Pharmacopoeia of the Russian Federation XI Monograph “Injectable pharmaceutical forms”

The requirements of the present General Pharmacopoeia Monograph do not apply to immunobiological medicinal products, human blood-containing medicinal products, and radiopharmaceutical preparations designed for parenteral administration.

Homeopathic solutions for injection should additionally meet the requirements of the General Pharmacopoeia Monograph “Homeopathic solutions for injection”.

Pharmaceutical forms for parenteral administration are supplied as sterile dosage forms designed for administration to humans by means of injection, infusion, or implantation (involving impairment of the integrity of the skin or mucous membranes, not through the gastrointestinal tract).

Pharmaceutical forms for parenteral administration include:

- injectable and infusion pharmaceutical forms (solution for injection, emulsion for injection, suspension for injection, solution for infusion, emulsion for infusion);
- concentrates for injectable and infusion pharmaceutical forms;
- solid pharmaceutical forms designed for preparation of injectable and infusion pharmaceutical forms (powder; lyophilized substance, including “freeze-dried powder”);

– pharmaceutical forms for implantation (implant, tablet for implantation, etc.).

Solution for injection (including “gel for injection”) – an aqueous or non-aqueous solution of a drug substance (or drug substances) in an appropriate solvent, designed for administration by injection.

Emulsion for injection – an “oil-in-water” or “water-in-oil” emulsion designed for administration by injection.

Suspension for injection – a suspension designed for administration by injection.

Depending on the method of administration, injectable pharmaceutical forms are classified into subcutaneous, intramuscular, intravenous, intra-articular, intracardiac, intracavitary, subconjunctival, etc.

Solution for infusion – an aqueous solution for intravascular administration that have a volume of 100 mL or more.

Emulsion for infusion – an “oil-in-water” emulsion for intravascular administration that have a volume of 100 mL or more.

Concentrate for injectable or infusion pharmaceutical forms – a liquid pharmaceutical form that serves to obtain an injectable or infusion pharmaceutical form by dilution with an appropriate solvent.

Powder for injectable or infusion pharmaceutical forms – a solid fixed-dose pharmaceutical form with or without excipients, dry and friable, which is designed for preparation of a solution or suspension for parenteral administration.

Lyophilized substance (including “freeze-dried powder”) for injectable or infusion pharmaceutical forms – a solid fixed-dose pharmaceutical form obtained by lyophilization, which is designed for preparation of a solution or suspension for parenteral administration.

Pharmaceutical forms for implantation – pharmaceutical forms for implantation and releasing a drug substance (or drug substances) over a certain (long) period of time.

TECHNOLOGICAL SPECIFICS

Pharmaceutical forms for parenteral administration are subject to sterilization in accordance with the requirements of the General Pharmacopoeia Monograph “Sterilization” and directions included in the Pharmacopoeia Monographs.

Solvents

Water used in the preparation of parenteral pharmaceutical forms should meet the requirements of the Pharmacopoeia Monograph “Water for Injections”.

Apart from Water for Injections, acceptable aqueous solvents include isotonic sodium chloride solution, Ringer’s solution, 5 % glucose solution, etc.; permitted non-aqueous solutions include fatty vegetable oils and other organic solvents.

Unless otherwise specified in the Pharmacopoeia Monograph, vegetable oils to be used for preparation of pharmaceutical forms for parenteral administration should meet the following requirements: they should be transparent at 10 °C, have no odour or almost no odour and have no rancid odour. The acid number should not exceed 0.56, the saponification number should lie in the range of 185 to 200, and the iodine number should be from 79 to 141. Liquid synthetic mono- and diglycerides of fatty acids may be used as well; they should be transparent if cooled to 10 °C and have an iodine number not exceeding 140.

The composition of a complex solvent may include ethyl alcohol, glycerine, propylene glycol, macrogol 400, benzyl benzoate, benzyl alcohol, and some other substances.

Solvents used in the preparation of pharmaceutical forms for parenteral administration should meet the requirements of the Pharmacopoeia Monographs with regard to the “Bacterial endotoxins” or “Pyrogenicity” parameters.

Excipients

The composition of a pharmaceutical form for parenteral administration may additionally include antimicrobial preservatives, stabilizers, emulsifiers, solubilizers, and other excipients specified in the Pharmacopoeia Monographs.

Excipients included to augment the stability of active ingredients may in-

clude ascorbic, hydrochloric acid, tartaric, citric, and acetic acids, sodium carbonate and sodium hydrocarbonate, sodium hydroxide, potassium or sodium sulfite, sodium hydrosulfite or metabisulfite, sodium thiosulfate, disodium edetate, sodium citrate, sodium phosphate (monobasic or dibasic), antimicrobial preservatives: methyl parahydroxybenzoate and propyl parahydroxybenzoate, chlorobutanol, cresol, phenol, and others.

Unless otherwise specified in the Pharmacopoeia Monograph, the amount of excipients should not exceed the following concentrations: 0.01 % for substances containing mercury and cationic surfactants; 0.5 % for substances like chlorobutanol, cresol, and phenol; 0.2 % for sulfuric anhydride or equivalent amounts of potassium or sodium sulfite, bisulfite, and metabisulfite.

Preservatives should be added to multi-dose pharmaceutical forms for parenteral administration regardless of the sterilization method, except when the drug substance itself exhibits antimicrobial activity.

No antimicrobial preservatives should be added to parenteral pharmaceutical forms with a single dose exceeding 15 mL, except for special cases, as well as to medicinal products designed for intracavitary, intracardiac, intraocular injections, or injections delivering drugs into the cerebrospinal fluid.

Pharmaceutical forms designed for infusion should be isotonic to human blood in most cases, and they should contain no antimicrobial preservatives.

TESTS

All pharmaceutical forms for parenteral administration must pass the Sterility test, as required by the General Pharmacopoeia Monograph "Sterility".

Pharmaceutical forms for parenteral administration, as well as drug substances used to prepare them, are subject to testing for bacterial endotoxins or pyrogens. The test is carried out in accordance with the requirements of the General Pharmacopoeia Monograph "Bacterial endotoxins" or the General Pharmacopoeia Monograph "Pyrogenicity".

A test for abnormal toxicity should be carried out in accordance with the re-

quirements of the General Pharmacopoeia Monograph “Abnormal toxicity” for pharmaceutical forms for parenteral administration prepared from naturally occurring raw materials, for injectable and infusion pharmaceutical forms supplied in containers made of polymeric materials, and in some other cases, if required by the Pharmacopoeia Monograph.

Pharmaceutical forms for parenteral administration designed for intravascular administration and obtained from drug substances that may exert a depressor effect (substances of microbial or animal origin) are subject to testing for histamine and / or depressor activity in accordance with the General Pharmacopoeia Monographs “The test for histamine” and “The test for depressor substances”.

The “pH value” test should be performed for liquid pharmaceutical forms for parenteral administration in accordance with the requirements of the General Pharmacopoeia Monograph “Ionometry”.

Pharmaceutical forms for parenteral administration that contain antimicrobial preservatives and antioxidants should be tested for identity and quantified; the upper and lower limits of content should be specified in all cases.

Pharmaceutical forms for parenteral administration should pass the “Particulate matter” test performed in accordance with the requirements of the General Pharmacopoeia Monograph “Visible particulate matter” and the General Pharmacopoeia Monograph “Invisible particulate matter in pharmaceutical forms for parenteral administration”.

INJECTABLE PHARMACEUTICAL FORMS

Solutions for injection (including «*gels for injection*») should additionally pass the “Transparency” and “Colour intensity” tests.

Solutions for injection should be transparent (General Pharmacopoeia Monograph “Transparency and turbidity of liquids”). Colour intensity of solutions for injection is determined by comparison with reference standards in accordance with the General Pharmacopoeia Monograph “Colour intensity of liquids” or as required by the Pharmacopoeia Monographs.

Viscous solutions for injection and solutions of high-molecular-weight substances (including “gels for injection”) are controlled additionally in the “Viscosity” test.

Oily solutions for injection are additionally controlled in the “Density” test.

Emulsions for injection should display no signs of phase stratification, they should appear as “oil-in-water” emulsions and meet the requirements of the General Pharmacopoeia Monograph “Emulsions”. Additionally, emulsions for intravascular administration should be additionally controlled in the “Particle size” test. Unless otherwise specified in the Pharmacopoeia Monograph, the particle size should not exceed 5 µm.

Suspensions for injection should meet the requirements of the General Pharmacopoeia Monograph “Suspensions”.

Suspensions for injection should be additionally controlled in the “Particle size”, “Passage through needles”, and “Resistance to sedimentation” tests.

PHARMACEUTICAL FORMS DESIGNED FOR INFUSION

Pharmaceutical forms designed for infusion should meet the requirements established for solutions or emulsions for injection.

The labels of pharmaceutical forms designed for infusion should include the theoretical osmolarity value. When the theoretical osmolarity value cannot be calculated, the average osmolality value should be indicated in accordance with the General Pharmacopoeia Monograph “Osmolarity”.

Unless otherwise specified in the Pharmacopoeia Monograph, pharmaceutical forms designed for infusion should be tested for the presence of bacterial endotoxins in accordance with the requirements of the General Pharmacopoeia Monograph “Bacterial endotoxins”.

CONCENTRATES FOR INJECTABLE OR INFUSION PHARMACEUTICAL FORMS

Before use, concentrates are diluted to the specified volume using an appropriate sterile solvent. The solution obtained as a result of this dilution should meet the requirements established for injectable or infusion pharmaceutical forms.

Concentrates are evaluated in the “Transparency”, “Colour intensity”, and

“pH value” tests following dilution in the solvent and to the concentration specified in the Prescribing Information, unless otherwise specified in the Pharmacopoeia Monograph.

POWDERS AND LYOPHILIZED SUBSTANCES FOR PREPARATION OF INJECTABLE OR INFUSION PHARMACEUTICAL FORMS

To prepare injectable or infusion pharmaceutical forms, the contents of a medicinal product container are dissolved or dispersed in an appropriate sterile solvent immediately before administration. Obtained solutions or suspensions must meet all requirements established for solutions for injection or for suspensions for injection.

The “Transparency”, “Colour intensity”, “pH value”, and “Particulate matter” tests are carried out using the solution obtained by dissolution of the medicinal product in the solvent and to the concentration specified in the Prescribing Information, unless otherwise specified in the Pharmacopoeia Monograph.

If organic solvents are used in the manufacture of powders or lyophilized substances, their residual content should be controlled in accordance with the General Pharmacopoeia Monograph “Residual organic solvents”.

Powders and lyophilized substances for preparation of injectable or infusion pharmaceutical forms should meet the requirements of the General Pharmacopoeia Monograph “Powders”.

IMPLANTS

Implants have to be controlled for compliance with the requirements of the General Pharmacopoeia Monograph “Uniformity of dosage” and the General Pharmacopoeia Monograph “Weight uniformity of fixed-dose dosage forms”. Additionally, the size of the implant should be determined and the latter should be tested for release of the active substance (or active substances).

If the “Uniformity of dosage” test is performed, the “Weight uniformity” is not obligatory.

PACKAGING

According to the requirements of the General Pharmacopoeia Monograph

“Pharmaceutical forms”. Pharmaceutical forms for parenteral administration are supplied in vials, ampoules, syringes, cartridges, or polymeric containers. Packages should be made of sufficiently transparent materials that permit visual examination of the contents, with the exception of packaging for implants and other cases specified in the Pharmacopoeia Monographs.

The brand of glass and packing materials should be specified in the Pharmacopoeia Monograph. Materials used in the manufacture of packages and packing materials should produce no toxic effects.

The packaging and packing materials should ensure air-tightness of pharmaceutical forms for parenteral administration, display chemical and physical indifference to the medicinal product, and maintain its therapeutic activity, quality, and purity during preparation, storage, transportation, realization, and use.

Plastic materials or elastomers used in the manufacture of packing materials should be sufficiently dense and elastic to ensure integrity of the stopper during needle insertion and air-tightness of the container after removal of the needle.

Pharmaceutical forms for parenteral administration may be supplied either in single-dose containers (ampoules, cartridges, or pre-filled syringes) or in multi-dose packages containing several doses of the active ingredient.

The volume of a pharmaceutical form for parenteral administration supplied in a single-dose container should be sufficient for a single dose administration, but it should not exceed 1 litre. Pharmaceutical forms for parenteral administration designed for irrigation, haemofiltration, dialysis, or parenteral nutrition, are exempt from this volume limitation.

Pharmaceutical forms for parenteral administration designed for intracavitary, intracardiac, intraocular injections, or injections delivering drugs into the cerebrospinal fluid should be supplied in single-dose containers only.

Implants and tablets for implantation are packaged in individual sterile containers.

LABELING

According to the requirements of the General Pharmacopoeia Monograph “Pharmaceutical forms”. The package of a pharmaceutical form for parenteral administration should indicate the names and quantities of the active ingredients, a list of the names of all excipients included, and additionally, for infusion solutions, the quantities of all excipients included. If antimicrobial preservatives are used, the concentration of each antimicrobial preservative used should be indicated for all pharmaceutical forms for parenteral administration.

The osmolarity value should be specified for infusion solutions; additionally, if required by the Pharmacopoeia Monograph, the ionic composition should be indicated (in mmol/L).

If a package with a solvent is supplied along with a powder, freeze-dried powder, or freeze-dried substance designed for preparation of an injectable or infusion dosage form, the label of this package should indicate the composition of the solvent.

The labeling on the package of a concentrate for preparation of an injectable or infusion dosage form should additionally mention that the solution should be diluted before use in accordance with the Prescribing Information.

STORAGE

According to the requirements of the General Pharmacopoeia Monograph “Pharmaceutical forms” and the General Pharmacopoeia Monograph “Storage of medicinal products”. In a sterile package ensuring stability of the parenteral dosage form throughout the claimed shelf-life, away from light, in the temperature range of 8 to 15 °C, unless otherwise specified in the Pharmacopoeia Monograph.