

MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

GENERAL PHARMACOPOEIA MONOGRAPH

Abnormal toxicity

GPM.1.2.4.0004.15

Replaces the State Pharmacopoeia of the Russian Federation XII, Part 1 Monograph, GPM 42-0060-07

The present General Pharmacopoeia Monograph describes the method used to determine the abnormal toxicity of medicinal products. The test should be conducted on substances of natural origin, medicinal products obtained from human or animal blood, organs, and tissues, vegetable raw materials, microorganisms and their metabolic products during the manufacture of released dosage forms, mainly for parenteral administration. The main objective of the abnormal toxicity test is to reveal a medicinal product's toxicity exceeding a previously established acceptable level controlled by increasing mortality or unexpected (not permitted) manifestations of intoxication in animals. This test allows to demonstrate abnormal (increased) toxicity of a medicinal product that may be exhibited by the drug as a result of a presence of degradation products or undesirable impurities not allowed by the manufacturing procedure, transportation or storage conditions, following a change in the manufacturing process.

Test method

The test is carried out on 5 healthy white mice of either gender, with a body weight of 19 to 21 g, previously unused in experiments. The housing and feeding conditions should ensure normal vital functions of experimental animals.

The tested medicinal product is dissolved or diluted (if necessary) with 0.9 % sodium chloride solution for injection. The test dose should be contained in a

0.5 mL portion of the tested solution, which should be injected into the animal's caudal vein at a rate of 0.1 mL per second. The test dose should be specified in the Pharmacopoeia Monograph. The observation period should last 48 hours.

If the Pharmacopoeia Monograph contains different directions, they should be followed.

A medicinal product passes the test if none of the experimental animals dies within the established observation period.

If one animal dies, the experiment should be repeated on 5 mice with a mean body weight of 20.0 ± 0.5 g. If no mouse dies during the second test, the medicinal product has passed the test.

A medicinal product fails the test if more than one experimental animal dies within the established observation period.

Test for immunobiological medicinal products

The test is carried out on two animal species: on 5 healthy white mice with a body weight of 18 to 20 g and / or two guinea-pigs with a weight of 250 to 300 g. The animals' weight is determined on the first day of the experiment. The test should be conducted on healthy animals previously unused in experiments. The housing and feeding conditions should ensure normal vital functions of experimental animals.

Test on white mice

The tested medicinal product is administered to each of 5 experimental animals intraperitoneally at the maximum human single dose (but not more than 1.0 mL), unless otherwise specified in the Normative Document. A lyophilized medicinal product should be reconstituted with the supplied solvent according to the directions on the label. If the tested medicinal product is designed for intravenous administration, its abnormal toxicity should be determined for the intravenous route and the tested dose should not exceed 0.5 mL. A product administered intravenously should have a temperature of $36 \pm 1^\circ$ C.

The observation period should last 7 days. If the Pharmacopoeia Monograph contains different directions, they should be followed.

A medicinal product passes the test if the following conditions are fulfilled throughout the observation period:

- no experimental animal dies;
- none of the animals present with manifestations of intoxication;
- no weight reduction occurs in experimental animals compared with baseline.

If more than one animal dies, the medicinal product fails this test. If one animal dies, manifestations of intoxication develop, or a reduction in body weight is observed, the test should be repeated on twice as many animals. The medicinal product passes the test if no animal dies in the second group, no manifestations of intoxication develop, and no reduction in body weight is observed throughout the observation period.

Test on guinea-pigs

The tested medicinal product is administered to 2 experimental animals subcutaneously, at a dose equal to the maximum human single dose (but not more than 10 mL), unless otherwise specified in the Normative Document.

A lyophilized medicinal product should be reconstituted with the supplied solvent according to the directions on the label. If the tested medicinal product is designed for intravenous administration, its abnormal toxicity should be determined for the intraperitoneal route and the administered dose should not exceed 5 mL.

The observation period should last 7 days, unless otherwise specified in the Normative Document.

A medicinal product passes the test if the following conditions are fulfilled throughout the observation period:

- no experimental animal dies and none of the animals develops visible signs of disease;
- no weight reduction occurs in any of the experimental animals on the observation final day, as compared with baseline;

- none of the animals administered the tested medicinal product subcutaneously develops a necrosis or abscess at the administration site (the possibility of developing other manifestations of an administration site reaction should be specified in the Normative Document for the tested medicinal product).

The medicinal product passes the test if no animal develops manifestations of intoxication and no body weight reduction is observed.

If both animals die, the medicinal product fails the test.

If one animal dies or a disease, weight reduction, necrosis or abscess at the site of administration of the tested medicinal product is observed in at least one animal within the observation period, the test should be repeated on twice as many animals of the same species. The second test is considered satisfactory if the medicinal product meets the above requirements.

The medicinal product passes the test if no animal dies in the second group or no manifestations of intoxication develop and no reduction in body weight is observed throughout the observation period.