Heavy metals	**GM 1.2.2.2.0012.15** **Instead of SpH X** **Instead of SpH XI, ed. 1** **Instead of SpH XII, p. 1,** **GM 42-0059-07**

Methods for determination of heavy metal content (lead, mercury, bismuth, stibium, stannum, cadmium, silver, copper, molybdenum, vanadium, ruthenium, platinum, and palladium) in pharmaceutical products are based on formation of coloured sulphides. Aside from the listed elements, sulphides form iron in an amount over 0.05 % and arsenic.

Sodium sulphide solution (method 1) or thioacetamide reagent (method 2) are used as a source of sulphides.

After the reaction is completed, colour intensity of the test solution is compared with colour of the reference solution. The colouring of the test solution must not be more intense than the colouring of the reference solution.

Test is considered accurate if the reference solution has a slight brownish colour compared to blank solution.

Determination of heavy metal content in pharmaceutical products is possible for substances that form a clear, colourless solution and do not affect the interaction between metal ions with sulphide-ions due to complex-forming properties. In all other cases, determination is performed using sulphate ash or other mineralization technique of the test pharmaceutical product.

Maximum permissible content of heavy metals, testing method and conditions for preparation of the test sample must be indicated in the general monograph.

Determination of heavy metal content in pharmaceutical solutions

Test solution. 10 mL of a test solution prepared according to the general monograph.

Reference solution. Add 8 mL of water to 2 mL of lead ion reference solution (5 μg/mL).

Blank solution. 10 mL of water.

Note. If an organic solvent is used for preparation of test solution, then the test, reference and blank solutions are prepared using the same solvent.

Method 1. To the obtained solutions add 1 mL of diluted 30% acetic acid, 2 drops of 2% sodium sulphide solution, stir and compare colouring of solutions after 1 minute.

Slight opalescence of test solutions from precipitated sulphur is acceptable.

Method 2. To the obtained solutions add 2 mL of acetate buffer solution pH 3.5, stir, add 1 mL of thioacetamide reagent, stir and compare colouring of solutions after 2 minutes.

Determination of heavy metal content in ash residue of organic pharmaceutical substances.

Test solution. Ash residue obtained after ignition of a 1.0 g test sample (unless otherwise specified in general monograph) with presence of concentrated sulphuric acid, is treated while heated on a net with 2 mL of saturated solution of ammonium acetate neutralised by sodium hydroxide solution, 3 mL of water are added and the substance is filtered into a test tube through an ash-free filter previously rinsed with 1% of acetic acid solution first and followed by water. The crucible and the filter are rinsed with 5 mL of water by filtering it through the same filter into the same test tube.

Reference solution 1. Pour concentrated sulphuric acid in an amount collected for combustion of the test sample into a crucible and treat it the same way as the test sample, but use only 3 mL for rinsing the crucible and the filter, after which add 2 mL of lead ion reference solution (5 μg/mL) to filtrate.

Reference solution 2. Pour concentrated sulphuric acid in an amount collected for combustion of the test sample into a crucible, and treat it the same way as the test sample, but use only 3 mL for rinsing the crucible and the filter, after which add 2 mL of lead ion reference solution (10 μg/mL) are added to filtrate.

Blank solution. Prepare the same way as the test solution but omit the test sample.

Further, prepare determination using any of the above-described methods of determination of heavy metal content in pharmaceutical solutions.

Note. Iron salts contained in pharmaceutical products do not interfere with determination of heavy metals based on ash residue.

Lead ion reference solutions

100 μg/mL lead ion reference solution. Place 0.0799 g of lead nitrate into a 500 mL measuring tube and dilute in 50 mL of water with addition of 0.5 mL of concentered nitric acid, bring up to volume and stir.

10 μg/mL lead ion reference solution. Place 10.0 mL of lead ion reference solution (100 μg/mL of lead ion) into a 100 mL measuring tube, bring up to volume with water and stir. Shelf life is 1 day.

5 μg/mL lead ion reference solution. Place 5.0 mL of lead ion reference solution (100 μg/mL of lead ion) into a 100 mL measuring tube, bring up to volume with water and stir. Shelf life is 1 day.

The above-described methods are not selective and may only be used for determination of maximum total content of the listed heavy metals in pharmaceutical substances.

For quantitative determination of separate ions the following methods should be used:

- atomic absorption spectrometry;
- inductively coupled plasma-atomic emission spectrometry;

- inductively coupled plasma mass spectrometry.

Methods of quantitative determination of heavy metal content in pharmaceutical products should be validated and described in the general monograph.