RD 42-501-98

MINISTRY OF HEALTHCARE
OF THE RUSSIAN FEDERATION

RULING DOCUMENT (RD)

INSTRUCTIONS
for Inspection for Particulate Matter in Injectable Drugs

Official Edition

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RD 42-501-98

INTRODUCTION

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SUBMITTED BY: State Drug and Medical Equipment Control Administration

2. **APPROVED**: Deputy Minister of healthcare of the Russian Federation 07.07.98.
3. **FINALIZED** by the Pharmacopeia State Committee
4. **PUT INTO EFFECT** by a letter of State Drug and Medical Equipment Control Administration, dated _____, No._____
5. **REPLACES** I 42-3-85 and RDI 42-1-89

MINISTRY OF HEALTHCARE OF THE RUSSIAN FEDERATION

RULING DOCUMENT

Approved

Deputy of the Minister
of Healthcare of the Russian
Federation

(signed)
V.I. Starodubov

July 07, 1998

INSTRUCTIONS
for Inspection for Particulate Matter in Injectable Drugs
RD-42-501-98

Replaces I 42-3-85 and RDI 42-1-89

1. General Provisions

1.1. These Instructions establish the procedure of inspection for particulate matter for all injectable drugs, including infusion and injection solutions, blood preparations, blood substitutes, preserved blood and dry formulations used in the form of solutions. Injectable medicinal drugs in ampoules, vials, bottles, syringes and other glass or clear polymer containers are subject to inspection.

1.2. These Instructions are obligatory for all enterprises and companies manufacturing and controlling the above-stated products, irrespective of their departmental affiliation or property category.

1.3. Particulate matter shall mean foreign insoluble particles (with the exception of gas bubbles) that may accidentally be present in drugs.

1.4. Sample shall mean the number of ampoules, vials, bottles and other containers that need to be taken for inspection from each batch of finished products.

1.5. Inspection for particulate matter takes into account the volume of injectable drug. Small volume drugs ≤100 ml, large volume drugs >100 ml whether they are formulated as solutions or obtained by dilution of dry medicinal drugs.

1.6. Inspection for particulate matter must be performed at conditions excluding the risk of contamination of inspected samples with foreign particles.

1.7. Inspection and counting of the number of particles may be performed using three methods:

a) Visual inspection
b) Counting-Photometric
c) Microscopic

2. Visual Inspection

2.1. Inspection Conditions

2.1.1. The room for visual control of injectable drugs for particulate matter must be protected from direct sunlight.

2.1.2. The work station of inspector must be equipped with a desk according to GOST 12.2.032-78 and a light source.

2.1.3. Visual control of injectable drugs is performed by inspector by the unaided eye against black and white backgrounds. The inspection zone must be lighted with electric glow lamp of the corresponding power depending on the color grade of solutions (table 1). The light intensity in the inspection area must be at least 200 lux.

Table 1

Light Power at Visual Inspection

Color of Solutions	Light Power	
	incandescent electric lamp, W	fluorescent lamp, W
Colorless	60	20
Colored	100	30

Notes.

1. The “Colored” group includes colorless solutions in dimming glass vials and stained solutions in colorless glass vials, as well as solutions in limpid polymer containers.
2. For inspection using KVLC-10 assembly it is allowed to use a 40W incandescent lamp.

2.1.4. For inspection of liquid injectable drugs mechanical feed of ampoules, vials, bottles, syringes and other clear polymer containers to the inspection area with further transport to the further operation stages, is acceptable, as well as the use of various types of special assemblies for inspection ensuring quality inspection according to the present Instructions.

2.1.5. For visual inspection of injectable drugs the inspector must have a twenty-twenty vision. If required, vision may be corrected using glasses. The vision of inspector is checked by ophthalmologist at least once in every 6 months, which is marked in the medical record (“book”).

To relax the eye fatigue during inspection a 10-minute break is made every 1.5 hours.

2.1.6. The distance from the inspector's eyes to the inspection object must not exceed 25-30cm. The angle between the optical axis of viewing and light beam direction is around 90º. Inspector's eyes must be protected from direct light from the light source. The line of sight must be directed somewhat downwards, with inspector's head positioned vertically.

2.1.7. Conditions of visual control of dry injectable formulations:

- Prepare samples at class B rooms (OST 42-510-98);
- Open vials or ampoules, dilute drugs, test solvent in the drug at a class A workplace (laminar sterile air flow);
- An inspector must wear sterile gown and lint free tissue cap, e.g. art. 82138, latex gloves treated with a silicon emulsion solution KE-10-16 (weight fraction 0.1%) or similar;
- Treat the equipment, chemical glassware and work appliances with a detergent solution (e.g. Progress, weight fraction 0.1%), wash several times with hot water and rinse with purified water free of particulate matter.

2.2. Sampling

The number of samples taken from each batch of injectable drug depends on the physical state (solution or dry matter), volume (small or big), batch size, as well as method of inspection (destructive or non-destructive inspection).

2.2.1. For visual inspection of injectable drugs that do not require opening and dilution (non-destructive inspection), and for dry injectable formulations (destructive inspection) perform product sampling and assessment of inspection results using enhanced two-stage control according to GOST 18242-72 (reprint edition of 1983).

2.2.2. Small Volume Solutions (Non-Destructive Inspection)

2.2.2.1. From each batch take random samples in two stages: stage 1 and stage 2, according to Table 2.

Table 2

Sample Size for Visual Inspection of Small Volume Solutions and Assessment Parameters

Batch Size, units	Visual Inspection Stage	Sample Size for Visual Inspection, Units	Number of Containers with Small Volume Solutions with Particulate Matter	
			Acceptance Number	Rejection Number
1	2	3	4	5
1,201-3,200	First Total (two stages)	80 160	2 6	5 7
3,201-10,000	-''-	200 400	6 15	10 16
>10,000	-''-	315 630	9 23	14 24

2.2.3. *Large Volume Solutions (Non-Destructive Inspection)*.

2.2.3.1. From each batch take random samples in two stages: stage 1 and stage 2, according to Table 3.
2.2.3.2. At hemotransfusion stations for the purpose of inspection of injectable products the Quality Control (QC) department performs sampling of 10% of containers of a batch, at least 10 bottles. If at least one bottle with particulate matter is found, return the whole batch for repeated original inspection.

Table 3

Sample Size for Visual Inspection of Large Volume Solutions and Assessment Parameters

Batch Size, units	Visual Inspection	Sample Size for	Number of Containers with Small

	Stage	Visual Inspection, Units	Volume Solutions with Particulate Matter	
			Acceptance Number	Rejection Number
1	2	3	4	5
151-280	First Total (two stages)	20 40	0 1	2 2
281-500	-‘’-	32 64	0 1	2 2
501-1,200	-‘’-	50 100	0 2	2 3
1,201-3,200	-‘’-	80 160	0 3	3 4
>3,200	-‘’-	125 250	1 5	4 6

2.2.4. Dry formulations used in the form of solutions (destructive inspection).

2.2.4.1. From each batch take the first random samples according to Table 4.

Table 4

Sample Size for Visual Inspection of Dry Formulations and Assessment Parameters

Group of Products	Number of Vials (ampoules) in a Batch					
	≥ 35,000		≥ 70,000		≥ 105,000*	
	Number of Sample Groups	Number of Samples	Number of Sample Groups	Number of Samples	Number of Sample Groups	Number of Samples
1	2	3	4	5	6	7
1. Products for intravenous injections, with an indication “for injections” on the label: - ≤1g - >1 g (≤5g)	 1 1	 8 5	 2 2	 16 10	 3 3	 24 15
2. Products for intravenous injections, with an indication “for injections” on the label: - ≤1g - >1 g (≤5g)	 1 1	 5 3	 2 2	 10 6	 3 3	 15 9
*One group of samples is taken from every further 35,000 vials (ampoules)						

Notes

1. For products at a dosage of > 5 g the number of sampling groups, the number of samples in the sampling group and the acceptable level of particulate matter are specified in pharmacopoeia monographs.
2. For inspection at the State Scientific-Research Institute for Standardization and Control of Medicinal Drugs, at analytical laboratories, Centers of Drug Quality Control and at pharmaceutical warehouses of the Ministry of healthcare of the Russian Federation and other institutions, duplicated number of samples from one sampling group regardless of the group the product belongs to (see Table 4). If required, State Scientific-Research Institute for Standardization and Control of Medicinal Drugs may request additional samples on top of the duplicated number stated above.

2.2.5. Arbitrary Inspection

Product samples at an amount equal to the total sample size (for both inspection stages) and the corresponding analysis protocol are submitted for arbitrary inspection. If required, the state controlling entity may request additional number of samples.

2.3. Sample Preparation

2.3.1. Before performing a visual inspection of injectable drugs of large and small volume, that do not require opening or dilution, ensure that the surface of ampoules, vials, bottles, syringes or other clear polymer containers is clean and dry.

2.3.2. While performing a visual inspection of dry injectable formulations, the selected samples must be washed with particulate matter free purified water 3 times before opening. All labels and aluminum caps must be removed from the vials prior to washing. Dry the washed samples under a laminar sterile air flow.

2.3.3. For dilution of the product use purified water or another solvent specified in a pharmacopoeial monograph or in the drug prescribing information. The water or solvent must be preliminary filtered through a ≤1.2 μm membrane filter.

2.3.4. Visual inspection of the solvent is performed according to the following method: take 10 thoroughly washed 10 ml vials and using a washed injection syringe or filtering device like “Pistol” (Pistolet) inject about 5 ml of the solvent into each vial. Close the vials with rubber stoppers free of particulate matter and inspect the samples as specified in section 2.4.3. The solvent conforms if 9 of 10 vials do not contain visible particles.

2.3.5. Open the ampoules in the following way: Make an incision on the ampoule neck surface using a tungsten-carbide cobalt knife, then touch the rim of the incision with a red-hot molybdenum or wolframium wire. Cool and carefully remove the tip. Any other method of opening is possible, if it prevents penetration of particles of glass into the ampoule contents.

2.3.6. Injection of solvent into vials (ampoules) is performed through the neck using a filtering device like “Pistol” or a preliminary washed syringe. It is possible to inject the solvent through the stopper using a N 0840 needle syringe, preliminary washed from the outside and from the inside with particle-free purified water.

2.3.7. Inject the solvent at an amount sufficient for complete dilution of the drug (about half of vial or ampoule volume) or at a volume specified in the corresponding Ph Monograph or in the product prescribing information. Then close the vials with stoppers again. The product must be completely dissolved at shaking.

Notes.

1. Dissolve easily hydrolyzed immediately before inspection.
2. For high-molecular compounds (proteins, polysaccharides, glycoproteins etc.) the corresponding Ph Monograph or drug prescribing information must contain the information about solvents, pH, time and conditions of dilution and other factors that may influence the dilution process.

2.4. Analysis and Results

2.4.1. Small Volume Solutions

2.4.1.1. To view small volume solutions the time of inspection and the number of containers taken simultaneously, must correspond to those specified in Table 5.

Table 5

Sample Size, Duration and the Rate of Inspection

Number of Containers Taken for Inspection	Duration of Inspection of Simultaneously Taken Containers	Rate of Inspection, pcs./hour

Ampoules		Vials, Bottles		Syringes		Ampoules	Vials, Bottles	Syringes	Ampoules	Vials, Bottles	Syringes
Volume, ml	N, max.	Volume, ml	N	Volume, ml	N						
1	2	3	4	5	6	7	8	9	10	11	12
SMALL VOLUME											
1.0	15	5.0	5-6	1.0	7-8	15	8-10	15	<2,000	<1,700	< 870
2.0 – 3.0	13	30.0 – 50.0	2					15	<1,750	<600	
5.0	10	50.0 – 100.0	2					15	<1,600	<400	
10.0	9							15	<1,400	<300	
20.0 – 30.0	8							15	<1,250		
LARGE VOLUME											
		>100.0	1-2				<20			<300	

Notes.

1. The number of ampoules, simultaneously taken for inspection, must not exceed the number specified in the table, but usually it must be at least 50%.
2. In case it is required (for example, for the purpose of training), the number of simultaneously taken ampoules, vials, bottles, syringes is decreased by 2-3-fold.
3. The time of control is determined by the period, when inspectors only view injectable drugs in containers (illegible)[К.И.1] The inspector takes the containers, carries them to the inspection area and places into the tare. The duration of inspection must be at 40 – 60% of the total time of viewing, including secondary operations. With automatic feeding of containers to the inspection area, the duration of inspection must be at 70% of the total time. The duration of inspection of injectable formulations in dark glass and clear polymer containers, of colored solutions and non-aqueous solutions is increased by 20%, while the rate of inspection is decreased correspondingly.
4. The “Rate of Inspection” column includes containers with clear injectable drugs and with those containing particles, including the time needed for secondary operations. The rate of inspection in case of automated feeding of injectable products to the inspection area is increased by 20 – 50%.

2.4.2. Large Volume Solutions

2.4.2.1. To view large volume solutions the duration of inspection and the number of simultaneously taken bottles corresponds to the data in Table 5.

2.4.3. To view injectable drugs take the ampoules by tips, vials and bottles – by necks, syringes – by caps, place them to the inspection area in the upside down position and view them against black and white backgrounds. Then smoothly and avoiding shaking the product invert them and view again against black and white backgrounds. For products requiring opening and dilution the upside down part of inspection may be skipped.

2.4.4. Containers with injectable products with visible particles are considered rejected and placed into separate containers marked “rejected products”.

2.4.5. If at the first stage of inspection the number of containers with injectable drugs containing particles (see Tables 2 and 3) is equal or exceeds that specified in Column 5, the whole batch of the drugs is rejected. If the number of containers is less than the amount specified in Column 5, but exceeds the number specified in Column 4, the second stage inspection is performed on the same number of containers of the products analyzed (illegible)[К.И.2] of the drug after second stage of inspection is performed based on the number of units of products

[К.И.1] Неразборчиво.
[К.И.2] Неразборчиво.

containing particles in the total volume of the first and second sample groups according to Columns 4 and 5 in Tables 2 and 3.

2.4.7. The whole batch is rejected if the number of units of products with mechanic particles exceeds or equals to the number specified in Column 5 for the total volume of the first and second samplings.

2.4.8. In case of rejected products:
- QC department returns the products to the workshop (to the site);
- State regulatory authorities, pharmaceutical laboratories, analytical laboratories, Centers of drug quality control or laboratories of other institutions, and laboratory of pharmaceutical warehouses draw up a report and simultaneously inform the manufacturer and the State Drug and Medical Equipment s Control Administration under the Ministry of Healthcare of the Russian Federation in the appropriate manner.

2.4.9. The Principle of Inspection On-Site

2.4.9.1. The site performs a triple control of purity of injectable products.
Primary intradepartmental one hundred percent inspection, secondary – intradepartmental and tertiary selective control is performed by the QC inspector.

2.4.9.2. Primary inspection is performed on 100% of ampoules, vials, bottles, syringes and other polymer packages of injectable products that passed sterilization or prepared at aseptic conditions, before labeling and packaging.
Primary and secondary inspection is performed by viewers at the site. Viewers must have their numbers. The viewer's number is inserted into the packaging and stamped on the cap of the vial.
2.4.9.3. For the purpose of the secondary inspection from each batch that passed the primary control, an average sample of 5% of a 2000 batch of ampoules, vials, bottles, syringes, and 250 pcs. of larger batches is taken. If over 2% of ampoules, vials, bottles (illegible)[К.И.3] an average sample selected, is returned for repeated primary control.
Note. The requirements of secondary selective control do not apply to the blood service institutions (hemotransfusion stations).
2.4.9.4. The tertiary selective inspection is performed by QC inspectors. For the purpose of control select a mean sample of each batch of the manufactured product before labeling and packaging. The sample size for inspection of solutions for particles and assessment parameters must conform for small sized containers- to the data in Table 2 and for large sized containers – to the data in Table 3.
Note. For certain sites the Administration of the public control of drugs and medical devices of the Ministry of Healthcare of the Russian Federation may establish another procedure of in-house inspection of injectable drugs for particles.

2.4.10. *Dry formulations used as solutions*

2.4.10.1. For the purpose of the visual inspection view the total samples (depending on the number of vials (ampoules) in the batch according to Table 4) and calculate for each sample the number of particles. If more than 5 particles are found in a single vial (ampoule), no further counting is performed. In that case the result is determined as 7. Count the total number of particles in all samples of the first complete set of samples and divide it by the number of samples.
2.4.10.2. If products for intravenous administration with an indication on the label "for injections" contain:
- ≤ 15 particles - the batch is accepted after the first sampling;
- ≥20 particles – the batch is rejected after the first sampling;
- 16 to 19 particles – the second sampling is performed at the same amount (section 2.2.4.1) and viewed according to the same method.

If products for intramuscular administration contain:
- ≤ 23 particles - the batch is accepted after the first sampling;

[К.И.3] Неразборчиво.

- ≥29 particles – the batch is rejected after the first sampling;
- 24 to 28 particles – the second sampling is performed at the same amount (section 2.2.4.1) and viewed according to the same method.
In case the inspection is performed on two samples, the results for the first and for the second samples are added up.

If products for *intravenous* administration with an indication on the label "for injections" contain:
- ≤ 34 particles - the batch is accepted ;
- ≥35 particles – the batch is rejected ;

If products for *intramuscular* administration contain:
- ≤ 52 particles - the batch is accepted ;
- ≥53 particles – the batch is rejected.

2.4.10.3. If just one particle of glass is found in the total sample, additional samples are taken in the same amount.
The batch is considered accepted, if no particles of glass are found in any of the vials (ampoules) in the additional sample.

3. Counting-Photometric Method of Inspection

3.1. Inspection Conditions

3.1.1. Perform the analysis using devices based on the light-obscuration and allowing of automatically determining particle size, the number of particles of the corresponding size. For example, light obscuration particle count analyzers FC-151, FC-151.1 or A03-101.

3.1.2. The instrument-aided inspection is performed at conditions described in section 2.1.7.

3.2.1. *Small Size Solutions*

3.2.1.1. Out of each batch randomly select a sample of 8 vials (ampoules).

3.2.2. *Large Size Solutions*

3.2.2.1. Out of each batch randomly select the first sample of 3 vials (if the volume of the solution is less than 500 ml) or 2 vials (if the volume of the solution is 500 ml and more).

3.2.3. *Dry Formulations Used as Solutions*

3.2.3.1. Sampling is performed according to section 2.2.4.1.

3.3. Analysis and Results

3.3.1. The analyzer sensitivity is performed every time it is switched on, when changing one liquid analyzed for another one, and every 4 hours in case of continuous work of the device. Before inspection a blank test is performed to control the purity of air in the working area, of the chemical glassware and solvent used. Using a cylinder measure 50 ml of the solvent (section 2.3.3) and transfer the measured amount into the analyzer glass. Analyze 4 10 ml samples, discard the result for the first sample. The test conditions are considered satisfactory, if every one in three samples contain ≤ 2 particles 25μm in size. Otherwise the purity of air is controlled using an air dust load analyzer A3 and repeat the steps of preparation of glassware and solvent (sections 2.1.7, 2.3.3, 2.3.4) until complying results are obtained.

3.3.2. *Small Size Solutions, Including Dry Formulations for Injections Administered in the Volume of ≥100 ml after dilution.*

3.3.2.1. Carefully shake samples or aliquots for obtaining the total volume of 50 ml for one sample according to sections 2.3.2, 2.3.3, 2.3.6 and 2.3.7 and transfer into a measuring cylinder, then bring to the volume of 50 ml with solvent (Section 2.3.3). In case of need extract the solutions from the ampoules using a syringe, that had been preliminary prepared (illegible)[К.И.4] into the analyzer measuring glass. Set on the dosing block of the device the number of the samples being analyzed (10 ml). Turn on the mixer and in 2-3 minutes (after removal of bubbles of air) analyze sequentially 4 to 5 samples.

[К.И.4] Неразборчиво.

3.3.2.2. Results are treated in the following way: results for the first sample are discarded; for each successive sample record the result of count of the total number of particles of ≥5μm, as well as of ≥25 μm. Then calculate the arithmetical mean for results for all samples on both standardized particle size ranges.
The average number of particles in one ampoule (vial), for one of the standardized sizes (C vol) is calculated according to the following formula:

$$Cvol = \frac{Cav.sample \times Vsol}{Vsample \times Nvol.}$$, where

$C_{av.sample}$ – is an arithmetic average number of particles of one of the standardized sizes contained in one sample;
$V_{sol.}$ – the total volume of the tested solution, ml;
V_{sample} – volume of one controlled sample, ml;
N_{vol} – number of ampoules (vials) taken for analysis

3.3.2.3. If not otherwise stated in Ph. Monographs, on average, in one container the number of particles of ≥5 μm must not exceed 6,000, including NMT 600 particles of ≥ 25 μm. Otherwise no secondary analysis is performed and the batch is rejected.

3.3.3 *Large Size Solutions, Including Dry Formulations Administered at >100 ml after Dilution*
3.3.3.1. From an individual sample transfer about 100 ml of thoroughly mixed solution into an analyzer measuring glass. Let the solution settle for 2-3 min. to remove air bubbles. Set the volume of samples analyzed in the dosing block of the device (10 or 25 ml), turn on the mixer and after 1-2 min. successively test 4-5 samples.
Discard the results of the first sample. For each successive sample record the result of count of the total number of particles of ≥5μm, as well as of ≥25 μm. Then calculate the arithmetical mean for results for all samples on both standardized particle size ranges.
The number of particles in one ml of the study drug for each of the standardized sizes (N)is calculated according to the following formula:

$$N = \frac{Nav.sample}{Vsample}$$, where

$N_{av.sample}$ – arithmetic average number of particles of one of the standardized sizes per one sample;
V_{sample} – sample volume, ml

3.3.3.3. If not otherwise specified in Monographs, on average one milliliter of the tested product the number of particles of ≥5μm must not exceed 100, including NMT 4 particles of ≥25μm. Otherwise repeated analysis is not performed and the batch is rejected.

4. Microscopic Method of Inspection

4.1. Inspection Conditions

4.1.1. Inspection using microscopic method is performed according to the conditions described in section 2.1.7.

4.1.2. Equipment:

- Filter assembly, for example, Millipore, 25 mm in diameter, with a glass vortex;
- Membrane filters (membranes), preferably with a net on the surface, e.g. of a HAWG type (0.45 μm pore size), Millipore;
- (illegible)[К.И.5]
- Object glasses;

[К.И.5] Неразборчиво.

- Petri dishes;
- Binocular microscope of MBC-1 type (x100 magnification).

4.1.3. Prepare the microscope for operation according to the requirements described in the MBC-1 Binocular Microscope Manual". Using object micrometer determine the graduation of the ocular micrometer.

4.1.4. Prepare the solvent according to sections 2.3.3 and 2.3.4.

4.2. Sampling Procedure

The sampling procedure is performed according to section 3.2.

4.3. Analysis and Results

4.3.1. Preparation of Filtration Assembly and Blank Test

4.3.1.1. Wash the filtration assembly vortex and object plates with warm water and a detergent, e.g. "Progress", then successively rinse several times with warm tap water, purified water and particle free purified water (sections 2.3.3, 2.3.4).
Using a pipette place on the object plate silica emulsion in a thin layer, e.g. KE-10-16 for further secure fixation of membranes.

4.3.1.2. Before use rinse the membrane with a stream of particle-free purified water on both sides from top downward, holding it with forceps in a vertical position.
Then place the membrane into a filter holder and accurately set the vortex avoiding touching the surface of the membrane.

4.3.1.3. Before starting the operation perform a blank test for the membrane, vortex and purified water preparation quality control. For that pour into the filter holder vortex about 30 ml of particle-free purified water. Filter water under vacuum. Then switch off vacuum, carefully remove the vortex, accurately (illegible)[К.И.6] left in the Petri dish to dry the membrane.

4.3.1.4. Place the object plate and the membrane on the object table of the microscope, set the required magnification.
Set the light source sidewise so that the ray of light falls on the membrane surface under an angle of 10-20º. Adjust the light and focus the membrane to obtain the maximum sharpness of the visible particles.

4.3.1.5. Count the particles and determine their size along the whole surface of the membrane, shifting it from left to right and from top to bottom under the microscope lens. The particle size shall mean the maximum diameter of particles or the maximum linear size. The maximum number of >25μm particle size is 5. If a larger amount of particles is observed, repeat the preparation of equipment and purified water to obtain the required result.

4.3.2. Small Size Solutions, Including Dry Formulations for Injections Administered in the Volume of ≥100 ml after dilution

4.3.3. Invert the container with the drug solution 10 times and transfer the contents to the filter holder vortex. Then rinse the container with particle free water and discharge it to the vortex. Handle the other samples of the same batch in the same way. Then filter the solution under vacuum conditions. After completion of filtration rinse the membrane and the walls of the vortex with 3-5 portions of 5 ml of particle-free purified water. Filter the contents of the vortex under vacuum, count the particles and determine their size as described in sections 4.3.1.3 – 4.3.1.5.
Record the particles in the following ranges:
- 5-25 μm
- >25μm.
Count the total and the average (calculated for one container) number of particles of each range.

[К.И.6] Неразборчиво.

4.3.2.2. If not otherwise specified in Monographs, on average, in one container the number of particles of 5-25 μm in size must not exceed 5,000, including NMT 500 particles of 25μm. Otherwise no repeated analysis is performed and the batch is rejected.

4.3.3. *Large Size Solutions, Including Dry Formulations for Injections Administered in the Volume of ≥100 ml after dilution*

4.3.3.1. Invert the container with the drug solution 10 times, take 25 ml of the solution with a pipette and transfer the contents to the filter holder vortex. Filter the solution under vacuum conditions. After completion of filtration rinse the membrane and the walls of the vortex with 3-5 portions of 5 ml of particle-free purified water. Filter the contents of the vortex under vacuum, count the particles and determine their size as described in sections 4.3.1.3 – 4.3.1.5.
Perform the same steps with other samples of the same batch.
Record the particles in the following ranges:
- 5-25 μm
- >25μm.
Count the total and the average (calculated for one container) number of particles of each range. Out of the average number of particles of >25μm in size abstract the number of particles of > 25μm of the same range present in the water or in the solvent during blank test (section 4.3.1.3).

4.3.3.2. If not otherwise specified in Monographs, on average, 1 milliliter of the tested product the number of particles of 5-25 μm must not exceed 50, and the number of particles of >25 μm – 3 particles. Otherwise no repeated analysis is performed and the batch is rejected.
The microscopic method allows establishing the nature of particles in injectable drugs, which is particularly important for drug manufacturers, as it helps to identify and in certain cases eliminate the sources of contamination. As the most objective method, it may be used as arbitrary.

Head of the Drug and Medical Equipment State Control Administration (signed) R.U. Khabriev

MINISTRY OF HEALTHCARE OF THE RUSSIAN FEDERATION
(Minzdrav of Russia)
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27.07.98 No. 29-4/1587

Company Heads

Heads of Regional Analytical Laboratories (Drug Quality Control Centers)

Hereby the Drug and Medical Equipment State Control Administration informs you that effective from 01.11.98 the Ruling Document RD 42-501-98 “Instructions Inspection for Particulate Matter in Injectable Drugs” approved by the Ministry of Healthcare of the Russian Federation on 07.07.1998. This Ruling Document replaces the document I 42-3-85 “Interim Instructions for Inspection of Injectable Solutions for Particles” and RDI 42-1-89 “Instructions for Particle Inspection in Dry Formulations Intended for Injections, Used as Solutions”.
The quality control of drugs manufactured from 1.11.98 must be performed according to the specified RD.

Appendix: RD – 19 pages

Head of Administration (signature) R.U. Khabriev