THE EURASIAN ECONOMIC COMMISSION
BOARD

R E C O M M E N D A T I O N

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On Requirements to Water for Pharmaceutical Use Utilized in Production of Medicinal Products

The Board of the Eurasian Economic Commission, in accordance with Article 30 of the Treaty on the Eurasian Economic Union dated May 29, 2014 and paragraph 3 of Article 3 of the Agreement on Common Principles and Rules of Circulation of Medicinal Products within the Eurasian Economic Union dated December 23, 2014,

in order to harmonize the legislation of the Member States of the Eurasian Economic Union with regard to elimination of differences in the requirements imposed on water for pharmaceutical use utilized in production of medicinal products,

r e c o m m e n d s that the Member States of the Eurasian Economic Union, upon expiration of 6 months from the date of publication of this Recommendation on the official website of the Eurasian Economic Union, conform to the Requirements to water for pharmaceutical use utilized in production of medicinal products, according to the Annex, when manufacturing medicinal products for medical use.

Chairman of the Eurasian Economic Commission Board T. Sargsyan

ANNEX
to the Recommendation of the
Eurasian Economic Commission
Board No. 31
dated December 13, 2017

R E Q U I R E M E N T S
to Water for Pharmaceutical Use Applied in Production of Medicinal Products

I. General provisions

1. These Requirements have been designed to harmonize the laws of the Member States of the Eurasian Economic Union (hereinafter referred to as the Member States) in the sphere of circulation of medicinal products with the statutory power of the European Union in this sphere, taking into account the requirements of the World Health Organization.

2. These requirements are applied by enterprises of the pharmaceutical industry:

a) when using water of different categories in production of pharmaceutical substances, as well as medicinal products for medical use and veterinary medicinal products (hereinafter referred to as medicinal products);

b) when applying the Rules of good manufacturing practices of the Eurasian Economic Union, approved by the Decision of the Council of the Eurasian Economic Commission No. 77 dated November 3, 2016, (hereinafter - the Rules), in designing (development, installation) and operating systems for production, storage and distribution of water for pharmaceutical use in the form of an unpackaged product.

3. The regulated object of these Requirements is water for pharmaceutical use.

4. Water is one of the main products used in the pharmaceutical industry, it may be present as an excipient or used for preparing medicinal products for application, during the synthesis process, during the production of finished products or as a cleaning agent for cleaning (washing) containers, equipment, primary packaging materials, etc. Depending on various pharmaceutical applications, water of various categories is required.

II. Drinking water requirements

5. Drinking water requirements are not listed in the Pharmacopoeia of the Eurasian Economic Union approved by the Eurasian Economic Commission (hereinafter referred to as the Pharmacopoeia of the Union). Drinking water must conform to the requirements of regulatory documents approved by the authorized bodies of the Member States in relation to its quality attributes. Drinking water can be used in chemical synthesis processes, and in the early stages of cleaning the equipment of pharmaceutical productions, in case of no particular specifications or requirements stipulating that water of a higher quality category must be used. To obtain pharmacopoeial quality water it is allowed to use drinking water.

6. Drinking water is used unmodified, except for the cases of limited treatment of water obtained from a natural reservoir source (for example, from a well, pond, river, lake and sea). The condition of such a source provides for treatment that is required to ensure safety of water when consumed by people (drinking). Conventional water treatment includes desalination, softening, removal of specific ions, partial purification and antimicrobial treatment.

7. Drinking water obtained from public water supplies is usually a combination from more than one natural source. This water can be supplied from an external source (e.g., municipal water system), or its required quality can be achieved by appropriate treatment on site. Drinking water must be

supplied under continuous positive pressure in the pipeline system, without the defects that may lead to contamination of the pharmaceutical product.

8. Public water supply organizations perform trials and guarantee that the water supplied is of drinking water quality. Such trials are usually conducted with regard to the water obtained from the source of this public water supply organization.

9. The manufacturer of medicinal products is responsible for ensuring that the water source supplying purified water production system meets the requirements to drinking water quality.

If water treatment system is used at first to achieve the quality of drinking water and, accordingly, purified water, such water treatment site is identified and validated in accordance with the laws of the Member States.

10. In case that drinking water is used at certain stages of pharmaceutical production or is the source for the production of higher quality water for pharmaceutical use, then the water source is periodically tested by the manufacturer's quality assurance department to ensure that the quality of the drinking water meets the established requirements.

III. Categories of water for pharmaceutical use

11. Water for pharmaceutical use shall conform to the requirements set forth by the Pharmacopoeia of the Union, as well as pharmacopoeias of the Member States. Pharmacopoeia of the Union contains requirements to water of the following categories:

a) purified water;

b) highly purified water;

c) water for injection.

1. Purified water

12. Purified water in the form of unpackaged product is used for the production of medicinal products, where the water is not subject to requirements for sterility and/or apyrogenicity.

13. Purified water in the form of unpackaged product is made from water with at least drinking water quality established by the authorized body of the Member State and must correspond to the pharmacopoeial requirements to chemical and microbiological purity with the corresponding levels of alarm and action. This water must be protected from secondary contamination, reproduction and proliferation of microorganisms. The areas of its application are determined on the basis of a risk assessment proceeding from the information on the water production system. The alarm levels for the system of production, purification, storage and distribution of water for pharmaceutical use are determined based on the study of this system by the manufacturer of the pharmaceutical products.

14. Purified water in the form of unpackaged product is produced by methods of ion exchange, reverse osmosis, ultrafiltration and/or electro-deionisation (EDI), as well as distillation from water that meets drinking water quality requirements established by the legislation of the Member States.

2. Highly purified water

15. Highly purified water in the form of unpackaged product is intended for the production of medicinal products using water of higher quality than purified water, except when only water for injection must be used.

16. Highly purified water in the form of unpackaged product is produced from water that has at least drinking water quality established by the authorized body of the Member State. Such water shall conform to the

requirements imposed on the quality of water for injection (including limit for the content of bacterial endotoxins), but the preparation process of highly purified water may vary. Highly purified water in the form of unpackaged product must also be protected from secondary contamination, reproduction and proliferation of microorganisms. Identical pharmacopoeial microbiological requirements are imposed on highly purified water in the form of unpackaged product and water for injection in the form of unpackaged product.

17. Modern methods of highly purified water production include a two-stage reverse osmosis along with other appropriate methods (e.g., ultrafiltration and deionization).

3. Water for injection

18. Water for injection is used as a solvent in the production of medicinal products for parenteral use (as water for injection in the form of unpackaged product or as sterile water for injection, used to dissolve or dilute pharmaceutical substances or medicinal products for parenteral administration before applying). Water for injection in the form of unpackaged product is not sterile water and the final dosage form, it is an intermediate unpackaged product and is suitable for use as an ingredient in the formulation of medicinal products. Such water is water for pharmaceutical use of the highest quality.

19. Distillation method is validated as a stand-alone operation. Water for injection in the form of unpackaged product is produced from water, corresponding to the quality of drinking water, or water purified by distillation using the equipment, the parts of which, contacting with water, are made of neutral glass, quartz glass or suitable metal. Such equipment shall include an effective device for drop trapping. The method of two-stage reverse osmosis can also be used. Proper maintenance of the equipment is also necessary.

20. Purity control of water for injection is aimed at ensuring stable microbiological water quality with regard to removal of bacteria and bacterial endotoxins. When producing and storing water for injection, the manufacturer of pharmaceutical products must ensure control and monitoring of the total amount of viable aerobic microorganisms. Water for injection should withstand tests with regard to purified water, as well as comply with the additional requirements imposed on the content of bacterial endotoxins (less than 0.25 IU/ml), specific electrical conductivity and content of total organic carbon.

4. Other categories of water

21. If a specific process requires water of a special quality category other than those provided for by the Pharmacopoeia of the Union, as well as the pharmacopoeias of the Member States, specification must be developed for such water in accordance with the manufacturer's quality assurance system. This water must meet at least the pharmacopoeial requirements to the category of water for pharmaceutical use, necessary for the dosage form of the medicinal product used or a specific stage of the production process.

IV. Using water of various categories for the production of medicinal products

22. Validation and qualification of systems for production, storage and distribution of water for the production of medicinal products are a fundamental part of the Rules and form an integral part of inspection for compliance with the requirements of the Rules. Categories of the water used at various stages of production of pharmaceutical substances and medicinal products should be described in the pharmaceutical part of the registration dossier in accordance with Annex No. 1 to the Rules of registration and

examination of medicinal products for medical use, approved by the Decision of the Council of the Eurasian Economic Commission No. 78 dated November 3, 2016.

23. When water of a certain category is used, the characteristics and intended use of the intermediate or final product and the stage of the production process must be taken into account.

1. Water present as an excipient in the final formulation

24. The minimum acceptable quality of water for manufacturing sterile medicinal products is given in Table 1. Water for injection is required to produce drugs intended for parenteral administration, including solutions for hemofiltration and hemodialysis filtration, as well as for peritoneal dialysis.

Table 1

The minimum acceptable quality of water
for manufacturing sterile drugs

Sterile medicinal products	The minimum acceptable quality of water
Parenteral	water for injection
Solutions for hemofiltration and solutions for hemodialysis filtration	water for injection
Solutions for peritoneal dialysis	water for injection
Solutions for ablution (irrigation)	water for injection
Ophthalmic	water for injection (purified water)
Nasal (ear) drugs	purified water
Drugs for external use	purified water

25. In the pharmaceutical industry, water for injection is often used to produce sterile ophthalmic, nasal or ear drugs and drugs for external use. In case of large amounts of industrial consumption highly purified water may be used.

26. The minimum acceptable quality of water for manufacturing non-sterile medicinal products is given in Table 2. With the exception of some inhaled drugs used with nebulizers, a valid category of water for all non-sterile medicinal products is purified water.

Table 2

The minimum acceptable quality of water
for manufacturing non-sterile drugs

Non-sterile medicinal products	The minimum acceptable quality of water
Drugs for oral administration	purified water
Solutions for inhalation	purified water*
Drugs for external use	purified water**
Nasal (ear) drugs	purified water
Rectal (vaginal) drugs	purified water

*Sterility and apyrogenicity requirements are imposed on the medicinal products used for treatment of certain diseases (e.g., cystic fibrosis), as well as liquid medicinal products in single and multi-dose containers that are administered by inhalation. In such cases, water for injection or highly purified water must be used.

**For some drugs (e.g., veterinary medicinal products for washing nipples) it may be acceptable to use drinking water in cases where this is justified and permitted, taking into account the variability of its chemical composition and microbiological quality.

2. The water used in the production process of pharmaceutical substances and medicinal products, excluding water, present as an excipient in the final formulation

27. An acceptable category of water largely depends on the stage at which it is used in the production process, subsequent manufacturing operations, as well as the nature of the finished product. Information on the acceptable water quality for the production of pharmaceutical substances, as well as for sterile and non-sterile medicinal products, is summarized in Tables 3 and 4.

Table 3

The minimum acceptable quality of water
used in the production of pharmaceutical substances

Production type	Product requirements	Minimum acceptable quality of water
Synthesis of all intermediate products for a pharmaceutical substance until the final stages of separation and purification	there is no requirement regarding sterility or apyrogenicity for the pharmaceutical substance or drug in which it will be used	drinking water*
Media for fermentation	there is no requirement regarding sterility or apyrogenicity for the pharmaceutical substance or drug in	drinking water*
Extraction from plants	there is no requirement regarding sterility or apyrogenicity for the pharmaceutical substance or drug in which it will be used	drinking water
Final separation and purification	there is no requirement regarding sterility or apyrogenicity for the pharmaceutical substance or drug in which it will be used	drinking water
Final separation and purification	pharmaceutical substance is not sterile, but is intended for use as part of a sterile drug for non-parenteral administration	purified water
Final separation and purification	pharmaceutical substance is sterile, but is not intended for injection	purified water
Final separation and purification	pharmaceutical substance is not sterile, but is intended for use as part of a sterile drug for parenteral administration	purified water with endotoxin content limit 0.25 IU/ml, control of specific microorganisms
Final separation and purification	pharmaceutical substance is sterile and apyrogenic	water for injection

*Purified water should be used, if technical requirements are imposed with regard to chemical purity.
**The applicant must prove that the possible changes in water quality (particularly with regard to mineral composition) will not affect the composition of the extract.

Table 4

The minimum acceptable quality of water used for the production of medicinal products, but missing in the final composition of the medicinal product

Production stage	The minimum acceptable quality of water
Granulation	purified water
Applying coating to tablets	purified water
Before non-sterile lyophilization	purified water
Before sterile lyophilization	water for injection

3. The water used for cleaning (washing) equipment, primary packaging and closure elements

28. During final cleaning (washing) of equipment and primary packaging (containers and closure elements), water of the same quality is generally used, as the water used at the final production stage of a pharmaceutical substance, or in the composition of a medicinal product as excipient. The minimum acceptable quality of water used for cleaning (washing) is shown in Table 5.

Table 5

Minimum acceptable quality of water used for cleaning (washing)

Product type	Cleaning (washing) equipment, primary packaging (containers, closure elements)	Minimum acceptable quality of water
Intermediate products and pharmaceutical substances	initial washing	drinking water
Pharmaceutical substances	final washing	water of the same quality as used in the production of pharmaceutical substances

Product type	Cleaning (washing) equipment, primary packaging (containers, closure elements)	Minimum acceptable quality of water
Non-sterile medicinal products	initial washing, including cleaning containers and closure elements on site (if necessary)	drinking water
Non-sterile medicinal products	final washing, including cleaning containers and closure elements on site (if necessary)	purified water or water of the same quality, as used in the production of a medicinal product, or water of higher quality than purified water
Sterile drugs	initial washing, including cleaning containers and closure elements on site (if necessary)	purified water
Sterile drugs not intended for parenteral administration	final washing, including cleaning containers and closure elements on site (if necessary)	purified water or water of the same quality, as used in the production of a medicinal product, or water of higher quality than purified water
Sterile drugs intended for parenteral administration	final washing, including cleaning containers and closure elements on site (if necessary)	water for injection

*For some containers (e.g., polymeric containers for eye drops) initial washing is not required, as it may in fact be counterproductive because washing can increase the amount of mechanical inclusions. In some cases (for example, in the blowing-dosing-sealing processes), washing is not allowed.
**If after cleaning the equipment is dried with 70 percent alcohol, it should be diluted with water of the same quality as water used for the final washing.
***If the subsequent stage of depyrogenation is applied, highly purified water may be used provided that appropriate justification and validation data are available.

V. Specifics of forming requirements to water use

29. Water is widely used as a raw material or initial substance for production, processing and creation of drug formulations. It has unique chemical properties due to its polarity and hydrogen bonds. This ensures the ability of water to dissolve, absorb or suspend many different compounds. Such compounds include pollutants (contaminants), which can be dangerous

by themselves or can interact with the substances used in the production of the drug, leading to health risks.

30. The main problem is water quality control in the process of production, storage and distribution, including control of microbiological and chemical quality. Unlike other ingredients of the product or process, if the water comes from a distribution system, the pharmaceutical manufacturer may not use it as a test object before use. At the same time, it is necessary to ensure water quality appropriate to the intended use. In addition, for microbiological testing periods of cultivation are required, and consequently, results can be obtained after using water.

31. Microbiological quality control of water for pharmaceutical use is carried out in the first place. Some microorganisms can breed in the media used for water treatment, and in water storage and distribution systems. Proper system design, regular sanitary treatment and adoption of appropriate measures to prevent microbial breeding and proliferation are critical for minimizing microbial contamination.

32. Depending on the method of application of medicinal products, different categories of water quality are required.

33. To ensure reliable production of water with the appropriate quality, systems of production, purification, storage and distribution of water for pharmaceutical use must be designed, installed, commissioned, tested and properly operated. The process of production, storage and distribution of water must be validated to ensure that it delivers the required performance and the quality of the water meets the requirements of the specification.

VI. General principles for designing and operating systems of production, purification, storage and distribution of water for pharmaceutical use

34. Systems of production, purification, storage and distribution of water for pharmaceutical use should be designed in such a way as to satisfy average and peak water demand during production. Depending on the planned future needs, the systems of production, purification, storage and distribution of water for pharmaceutical use should be designed taking into account the possibility to increase productivity or modify them. Systems of production, purification, storage and distribution of water for pharmaceutical use, regardless of their size and performance, should have appropriate recirculation or turnover to ensure proper chemical and microbiological control.

35. Commissioning systems of production, purification, storage and distribution of water for pharmaceutical use after initial validation (installation qualification (IQ), operational qualification (OQ), performance qualification (PQ)), as well as after any scheduled or unscheduled maintenance or modifications must be approved by the quality assurance department (QA), with change control documentation.

36. With regard to sources of drinking water for pharmaceutical production, and with regard to purified water, chemical, microbiological contamination and (optionally) contamination with endotoxins should be regularly monitored. Also, operation of systems of water purification, storage and distribution must be monitored. Records must be kept of the results of monitoring, trend analysis, and any actions taken.

37. If chemical sanitization is part of the biocontamination control program, validation must be carried out afterwards to confirm the efficiency of chemical sanitization and removal of substances used for chemical sanitization.

VII. Systems of production of water for pharmaceutical use

1. General description

38. Pharmacopoeial monographs do not establish valid methods of obtaining water for pharmaceutical use, excluding water for injection in the form of unpackaged product. When designing and operating systems of production of water for pharmaceutical use, selection of the production method or sequence of its stages must comply with the intended use of the water for pharmaceutical use utilized in the production process. When choosing the method of obtaining water for pharmaceutical use, the following must be taken into account:

a) specification for the quality of water for pharmaceutical use;

b) the amount of water for pharmaceutical use, utilized by the pharmaceutical manufacturer;

c) the quality of available drinking water and its changes with time (seasonal changes);

d) accessibility of auxiliary means (e.g., water for the operation of the system, electricity, heating steam, chilled water, compressed air, sewerage, ventilation) required to connect the system of production of water for pharmaceutical use;

e) sanitization strategy;

f) availability of equipment for production of water for pharmaceutical use on the market;

g) reliability and safety of operation of the equipment for treatment of water for pharmaceutical use;

h) capacity and efficiency of the systems for purification of water for pharmaceutical use;

i) ability to properly operate and maintain pharmaceutical water treatment equipment;

j) duration of operational use of pharmaceutical water production systems, in hours and days (days and years), and their planned downtime;

k) total costs over the lifecycle of the equipment (capital and operating costs, including maintenance).

39. Specifications for the pharmaceutical water production equipment and systems of storage and distribution of water for pharmaceutical use should take into account:

a) arrangement of the production area;

b) temperature range, in which the equipment and systems will operate;

c) risk of contamination of equipment, systems and products from materials contacting with water;

d) adverse effects of absorbent materials;

e) hygienic or sanitary version of the equipment and systems (if necessary);

f) corrosion resistance;

g) prevention of water leakage;

h) installation of systems preventing processes of microbial breeding and proliferation;

i) resistance to cleaning and sanitization agents (thermal and/or chemical);

j) sanitization strategy;

k) system load and performance indicators;

l) equipping the systems with the necessary measuring equipment, monitoring and sampling points in order to carry out the required monitoring of critical quality indicators of the entire system.

40. When designing, manufacturing and installing pharmaceutical water production equipment and systems of storage and distribution of water for pharmaceutical use, the following should be taken into account:

a) possibility of sampling;

b) technological area space, suitable for installation of the equipment and systems;

c) structural load on buildings;

d) ensuring the required access of staff to equipment and systems for their maintenance;

e) possibility of working safely with chemicals during regeneration and sanitization.

2. Production of drinking water

41. Drinking water is obtained from natural water sources, such as wells, rivers or ponds. There are no prescribed methods for processing the water used to obtain drinking water from a specific natural water source. Typical processes of obtaining drinking water used by pharmaceutical manufacturers or water supply organizations include:

a) desalination;

b) filtering;

c) softening;

d) disinfection or sanitization (for example, through the introduction of sodium hypochlorite (chlorine)) into the water;

e) iron (ferrous) removal;

f) precipitation;

g) reduction of concentration of specific inorganic and/or organic materials.

42. The drinking water quality should be monitored to account for environmental, seasonal or supply changes which have an adverse impact on the source water quality. Upon any change in the water source, processing technology or pharmaceutical water production system design, an additional test of drinking water quality should be conducted. To identify changes, trend analysis can be used. If drinking water quality varies considerably, but is still within the range indicated in the specification, direct utilization of this water as water for pharmaceutical use or water for subsequent stages of treating technological equipment at the industrial site must be checked, and the result of the check documented. If drinking water is obtained using a local natural water processing system, water treatment stages and the design of the pharmaceutical water production system, as well as changes in the system of obtaining water for pharmaceutical use or its operation shall be documented. Changes must be made to the system of obtaining water for pharmaceutical use or its operation after the completion of the trend analysis and approval of the changes by the quality assurance department of the pharmaceutical manufacturer in accordance with the change control procedures.

43. If drinking water is stored and distributed to technological areas (production sites) by pharmaceutical manufacturers, its storage and distribution systems must ensure the quality of this water established by Section III of these Requirements before use. After any storage it is necessary to test water quality in accordance with a specific method, if not experimentally justified otherwise. The water storage and distribution system operated by the pharmaceutical manufacturer should ensure sufficient circulation to prevent water stagnation, or recirculation of the water stored in it.

44. The system of obtaining drinking water is generally regarded as an "indirect effect system" and does not require routine testing. When

transporting unpackaged drinking water to the pharmaceutical manufacturer in a tank, the additional risks that are not associated with drinking water supplied by pipelines must be taken into account. Similar to the approach used for other raw materials, it is necessary to evaluate the supplier and ensure that the parameters of the system meet the mandatory requirements to the water sources established in the Member State, including validation (suitability confirmation) of the means of delivery.

45. Equipment and systems used to obtain drinking water must be suitable for water removal and sanitization. Storage tanks for drinking water should be properly closed with protected air valves, should ensure visual inspection of the interior and exterior of the tank and should be suitable for water removal, flushing and sanitization.

46. Particular attention should be paid to microbial contamination control of pre-treatment filters, coal layers and water softeners. When the system of pharmaceutical water storage and distribution is infected, formation of biofilms and microbial proliferation throughout the entire system are possible. To minimize microbial contamination, reverse flushing, chemical and/or thermal sanitization and frequent regeneration can be applied.

3. Obtaining purified water in the form of unpackaged product

47. To obtain purified water in the form of unpackaged product, any acceptable controlled technology or a sequence of treatment technologies can be used. When a water purification system is created, or specifications of the pharmaceutical manufacturer are determined, the following must be taken into account:

a) the quality of the source water used to obtain purified water in the form of unpackaged product and seasonal changes of this quality;

b) the amount of water needed by the pharmaceutical manufacturer;

c) the required water quality in accordance with the specification;

d) the necessary sequence of water purification stages;

e) power consumption;

f) degree of water pre-treatment needed to ensure that the final stages of purification are implemented;

g) carrying out optimization based on performance and efficiency of individual stages of the water treatment process;

h) properly located sampling points, designed to prevent the possible contamination;

i) providing individual stages of the process of obtaining purified water in the form of unpackaged product with appropriate tools and methods for measuring parameters such as flow rate, pressure, temperature, electrical conductivity, pH value and total organic carbon.

48. Such temperature-dependent systems as the system of ion exchange, reverse osmosis system and ultrafiltration system are subjected to microbial contamination, especially if the equipment is not functioning for a period of time when water consumption is missing or is at a low level. It is necessary to provide for appropriate microbiological control and sanitization methods for the system of water production, treatment, storage and distribution. At each stage of cleaning the system of water production, treatment, storage and distribution, a method of sanitization must be determined, which includes checking the fact of removing any of the substances used. Evidences supporting the efficiency of removing any of the substances used in sanitization are documented. In this regard, the following must be taken into account:

a) constant maintenance of the flow rate in the water production system above the minimum level;

b) ensuring temperature control in the water production system through a heat exchanger or cooling the water treatment premises (recommended temperature below +25°C) in order to minimize microbial growth;

c) the need to conduct a UV disinfection;

d) selection of the elements of the water production system to perform periodic thermal sanitization;

e) using chemical sanitization (including the use of substances such as ozone, hydrogen peroxide and/or peroxyacetic acid);

f) thermal sanitization at a temperature above +65°C.

4. Obtaining highly purified water in the form of unpackaged product

49. Requirements for obtaining purified water in the form of unpackaged product, established by subsection 3 of this Section, shall apply equally to obtaining highly purified water as unpackaged product.

5. Obtaining water for injection in the form of unpackaged product

50. Distillation is the preferred and safer technology based on phase transition and, in some cases, operation of the process ensuring equipment at high temperatures.

51. When designing a water purification system and establishing specification requirements to water for injection in the form of unpackaged product, the pharmaceutical manufacturer must take into account:

a) the quality of drinking water;

b) specification of water for injection with the required quality;

c) the amount of water for injection;

d) the optimal size of the distiller (distillers), adjustable (to prevent frequent start/stop cycles);

e) the need to purge the water production system and the need to discharge water;

f) cooling system (in order to prevent contamination).

52. Requirements for obtaining purified water in the form of unpackaged product, established by subsection 3 of this Section, shall apply equally to obtaining water for injection as unpackaged product.

VIII. Water storage and distribution systems

53. This Section defines the requirements to the systems of storage and distribution of purified water in the form of unpackaged product, highly purified water in the form of unpackaged product and water for injection in the form of unpackaged product. Water storage and distribution should be carried out in conjunction with its purification to ensure delivery of water with the consistent quality to the consumption points and optimal operation of the water treatment equipment. Water storage and distribution system should be seen as a key part of the whole water production system and should be fully integrated into the system of water purification.

54. After receiving water for pharmaceutical use, it can be used directly or sent via pipes to the storage tank for later distribution to the consumption points. The design of the water storage and distribution system should ensure prevention of breeding and proliferation of microorganisms, as well as repeated contamination after obtaining purified water in the form of unpackaged product, highly purified water in the form of unpackaged product and water for injection in the form of unpackaged product. The efficiency of such a system must be subjected to combined monitoring using the equipment incorporated into the system of water storage and distribution and external laboratory equipment.

1. The materials contacting with pharmaceutical water systems

55. This Section established the requirements to manufacturing systems for production of purified water in the form of unpackaged product, highly purified water in the form of unpackaged product and water for injection in the form of unpackaged product, and also to manufacturing systems for its storage and distribution.

56. When selecting materials contacting with water for pharmaceutical use, as well as the system of piping, valves and connectors, gates, diaphragms and measuring equipment, the following must be taken into account:

a) compatibility and suitability of materials must be acceptable throughout the range of operating temperatures and for all kinds of potential chemicals that will be in contact with the system of obtaining water for pharmaceutical use during its idle time, when functioning and conducting sanitization;

b) all materials contacting with water for pharmaceutical use, should not destroy when operating in the operating temperature range and under the temperature of sanitization of the pharmaceutical water production system;

c) purified water in the form of unpackaged product, highly purified water in the form of unpackaged product and water for injection in the form of unpackaged product feature high corrosion ability.

57. In order to prevent damage to the pharmaceutical water production system and water contamination when manufacturing pharmaceutical water production system, the appropriate materials should be used. The method of connecting manifolds and pipelines must be carefully controlled, and all connections and components of the pharmaceutical water production system must be compatible with the network of pipelines used. Plastic materials meeting the relevant requirements and stainless steel are suitable as a material for manufacturing pharmaceutical water production systems. Stainless steel of

at least AISI 316 grade (corresponding to steel grade 08X17H13M2) must be used. As a rule, stainless steel AISI 316L is used (corresponding to 03X17H14M3 steel), or stainless steel of higher quality.

58. The pharmaceutical water production system should be passivated (that is subjected to a process which gives metal or other substance resistance to reactions by changing the surface layer of the metal (substance), or the surface of the metal (substance) must be coated with a thin inert layer) after its initial installation or substantial modification. During accelerated passivation, the pharmaceutical water production system must first be completely cleaned, the passivating process must be conducted in accordance with the established and documented formal procedure.

59. Water is sensitive to microbial contamination, and biofilms are formed in its production systems in case of low temperatures of storage and distribution. The interior surfaces of the pharmaceutical water production system must be smooth. Cracks and roughness may be the source of contamination due to possible breeding of microorganisms and formation of biofilms. Cracks are places where surface corrosion may occur. The smooth inner surface of the pharmaceutical water production system should have an average arithmetic roughness value not exceeding 0.8 μm. When using stainless steel for the production of pharmaceutical water production systems, mechanical and electrical polishing technologies may be used. Electrical polishing increases the resistance of stainless material to surface corrosion.

60. The constituent parts of the pharmaceutical water production system should be easily assembled by welding in a controlled mode. Welding process control includes, at the very least, checking operator certification, checking documentation for preparation of welding operations, tests of working prototypes, logging welding operations and visual inspection of certain parts

of the welded seams (for example, 100% of the welded seams made by hand, 10% of the welds performed automatically).

61. The flanges, valves and connections used must take into account the possibility of conducting hygienic or sanitary treatment. Checks are performed, allowing to document the use of appropriate shutters and diaphragms, the correctness of their connection and seals. It is necessary to avoid threaded connections.

62. The components of the pharmaceutical water production system are documented, with the attachment of original documents or their copies certified by the pharmaceutical manufacturer.

63. The materials regarded as elements to be sanitized include stainless steel AISI 316L (low-carbon), polypropylene, PVDF and perfluoroalkoxy alcane polymers. The selection of the material is determined by the sanitization method established by the legislation of the Member States. Other materials (such as unplasticized polyvinyl chloride (PVC)) can be used to manufacture equipment used at the early stages of water purification (e.g., for softening).

The materials contacting with water for pharmaceutical use, must not contain chemicals extractable by water. Plastics must be non-toxic, compatible with the chemicals used and made from materials meeting at least the requirements of the Technical Regulations of the Eurasian Economic Union «On safety of materials contacting with food products», adopted by the Eurasian Economic Commission. Chemical and biological characteristics of these materials shall meet the requirements of the European Pharmacopoeia or, in the absence of such requirements - the requirements of the pharmacopoeias of the Member States.

64. Precautions must be taken by defining the operating limits for areas where water circulation is reduced and turbulent flow cannot be achieved. The minimum flow rate and the valid range of its change must be determined.

2. Monitoring the system of sanitization and biocontamination of water for pharmaceutical use

65. The systems for obtaining purified water in the form of unpackaged product, highly purified water in the form of unpackaged product and water for injection in the form of unpackaged product must be checked for proliferation of microorganisms during normal use, as well as equipped with the devices necessary for sanitization of the system after interfering in its operation or its modification. These devices are planned when designing the system, taking into account the interaction between materials and devices during sanitization.

66. The systems for obtaining water for pharmaceutical use, which are operated and maintained at elevated temperatures (above 70°C), are less susceptible to microbial contamination than systems that are operated and maintained at lower temperatures. If lower temperatures must be used due to the processes of water treatment used or thermal requirements to the consumed water, special precautions are taken to prevent microbial contamination in accordance with the requirements to monitoring contamination set forth in subsection 3 of this Section.

3. Requirements to water storage tanks

Capacity

67. Water storage tank capacity is determined according to the following requirements:

a) a water storage tank is selected optimally by volume based on the performance of the system of obtaining water for pharmaceutical use and

meeting the requirements of the pharmaceutical manufacturer to the maximum simultaneous water consumption;

b) a water storage tank must ensure continuity in the functioning of water treatment equipment during extended periods to prevent inefficiency and stressed state of equipment for water treatment, which arise when start/stop cycles of the water treatment equipment occur too frequently;

c) the capacity of a water storage tank must ensure sufficient short-term water reserve (reserve water volume) in the event of malfunction of the water treatment equipment or impossibility to obtain water resulting from sanitization or regeneration cycle. In determining such a reserve volume of water, it is necessary to take into account the possibility of ensuring a sufficient amount of water to complete the process cycle, wash the container with recirculation to minimize water stagnation or meet other alleged demands in water for pharmaceutical production.

Contamination control

68. Contamination control of the water storage tank shall be based on the following:

a) free space in the water storage tank is a risk zone, where drops of water and air may come into contact at temperatures allowing for the reproduction of microorganisms. In order to avoid this, dispensers or distribution devices are installed in the water storage tank, to ensure wetting of the surface of the tank under normal operation, chemical and/or thermal sanitization;

b) installation of nozzles is provided in the water storage tank to prevent stagnant areas where microbiological contamination can occur;

c) installation of air filters is provided in the water storage tank on air intake devices in response to a change in the internal liquid level. The specified

filters must hold bacteria, be hydrophobic and (preferably) suitable for testing integrity directly at the place of their installation. You can also test filters outside of the place of installation. Installation of heated air filters is provided for continuous maintenance of the water storage tank filters in a heated state, or systems using periodic sanitization by heating to prevent vapor condensation inside the filtering material that can lead to filter blockage and microbial growth, which may result in contamination of the water storage tanks;

d) pressure relief valves and protective membranes are installed in the water storage tank for protection against low or high pressure, which must be designed to allow for carrying out hygienic or sanitary treatment. These membranes are supplied with external gap indicators to control the loss of integrity of the system of water storage and distribution.

4. Requirements to water distribution pipeline systems

69. Distribution of purified water in the form of unpackaged product, highly purified water in the form of unpackaged product and water for injection in the form of unpackaged product is accompanied by the use of constant circulation of water in a closed system of pipelines. Microbial contamination control is carried out in the collector and in the closed system of water distribution pipelines. To apply a unidirectional water distribution piping system without water recirculation, the pharmaceutical manufacturer must submit a corresponding justification in the documents of the production site.

70. Filters in for pharmaceutical water distribution piping system and in consumption points must be avoided in order to prevent microbial contamination. Pharmaceutical water distribution piping system is designed so that water quality is maintained without the use of filters. If this is not possible,

it is necessary to thoroughly examine the reasons why water quality cannot be ensured.

5. Temperature control and heat exchangers

71. If heat exchangers are used for cooling or heating water for pharmaceutical use within the system of water storage and distribution, precautions are taken to prevent heating or cooling fluid from entering the water. Safer types of heat exchangers are used: double-pipe, plate-fin and shell-and-tube. If these types of heat exchangers are not used in the water storage and distribution systems, an alternative approach can be applied where engineering networks are operated and monitored at a lower pressure as compared to the pressure in the systems for obtaining water for pharmaceutical use (this approach is not used in systems obtaining water for injection in the form of unpackaged product). Heat exchangers are incorporated into the constantly circulating closed systems of pipelines or auxiliary pipelines to prevent water stagnation in them.

72. The cooling of water for pharmaceutical use for production purposes should be done within the minimum possible time. The number of cooling cycles and their duration must be confirmed during system qualification.

6. Circulation pumps

73. Circulating pumps are used in a version allowing for carrying out hygienic or sanitary treatment, with appropriate seals to prevent contamination of the system. When installed, the pumps are built and mounted in such a way as to avoid the formation of stagnant zones in the water storage and distribution system. In case of using parallel pumps, precautions are taken to prevent contamination of the water storage and distribution system (in particular, when there is water stagnation in one of the pumps).

7. Biocontamination control methods

74. Water production systems shall be subjected to sanitization using, if necessary, chemical or thermal methods. The method used and the conditions of treating the water production systems (periods and temperatures) must allow biocontamination control.

75. The following biocontamination control methods are used:

a) maintenance of the continuous circulation flow in the water distribution systems reduces formation of biofilms;

b) the design of the water production system ensures the shortest possible length of the pipeline system;

c) for water production systems that are dependent on the ambient temperature, pipelines are isolated from adjacent hot pipes;

d) dead-end branches in the piping systems are minimized and slightly exceed the triple size of the branch diameter measured from the inner diameter of the pipe wall to the centerline of the location of the valve where significant water stagnation is possible;

e) pressure gauges are isolated from the water production system with membranes;

f) washable diaphragm valves are used;

g) piping systems for steam sanitization have a tilt and provide the possibility to remove moisture.

76. The growth of microorganisms can be inhibited by:

a) UV radiation sources located in the piping system;

b) maintaining the water system in a heated state (at temperatures above 70°C);

c) periodic sanitization of the water production system using hot water (recommended temperature above 70°C);

d) periodic sanitization of the water production system using overheated hot water or clean steam;

e) regular chemical sanitization using ozone or other suitable chemicals with confirmation of the removal of these substances before using the water. Ozone can be effectively removed by UV radiation.

IX. Operation issues of pharmaceutical water production, purification, storage and distribution systems

1. Start-up and commissioning of pharmaceutical water production, purification, storage and distribution systems

77. For successful validation of pharmaceutical water production, purification, storage and distribution systems, it is necessary to ensure planning, clear and thorough documentation of commissioning and qualification of water production systems.

78. The commissioning of pharmaceutical water production, purification, storage and distribution systems includes preparation of these systems for operation, setting system efficiency parameters, as well as monitoring, configuration, and registration of all parameters specified. The quality of the commissioning works with regard to pharmaceutical water production, purification, storage and distribution systems performed during validation, the supporting data and documentation must comply with the requirements established by the validation plan.

2. Qualification of pharmaceutical water production, purification, storage and distribution systems

79. All systems of production, purification, storage and distribution of drinking water (purified water in the form of unpackaged product, highly purified water in the form of unpackaged product and water for injection in the form of unpackaged product) have a direct impact on the quality of the

resulting water, so they must be qualified. Qualification of the systems must be performed after standard design validation procedures or design qualification (DQ), installation qualification (IQ), operational qualification (OQ), or performance qualification (PQ).

80. These Requirements do not contain standard requirements to the normal stages of design qualification (DQ), installation qualification (IQ), operational qualification (OQ), but provide for a separate approach to performance qualification (PQ), which is used for pharmaceutical water production, purification, storage and distribution systems to demonstrate their stable and reliable operation.

81. Water source tests should be included in the design validation program and should be conducted within the framework of routine monitoring. The source water must meet drinking water quality requirements and specifications of the manufacturer of medicinal products.

The reliability and safety of pharmaceutical water production, purification, storage and distribution systems in case of operation over a long period are confirmed in 3 stages.

3. Confirmation of reliability and safety of pharmaceutical water production, purification, storage and distribution systems (stage I)

82. For 2 weeks, on a daily basis, 1 time per day or continuously, the quality of the drinking water supplied to the water production, purification, storage and distribution system is monitored. During this period, the system must operate continuously without switching off or operational deviations. Typically, the water obtained during this period is not used for the production of medicinal products. The tests include the following activities:

a) chemical and microbiological tests in accordance with the established plan;

b) sampling or continuous monitoring of drinking water supplied during the day to verify its quality;

c) sampling or continuous control after each cleaning process stage;

d) sampling or continuous control at each point of consumption and at other established sampling points;

e) development of appropriate operating limits;

f) development and implementation of procedures for operation, cleaning, sanitization and maintenance of the system;

g) attestation of conformity of the quality and quantity of the obtained and distributed water to the relevant requirements;

h) using and improving standard operating procedures (hereinafter referred to as SOPs) for operation, cleaning, sanitization of water production, purification, storage and distribution systems and operation in emergency situations;

i) checking alarm levels;

j) development and improvement of a procedure for the assessment of possible malfunctions during testing.

4. Confirmation of reliability and safety of pharmaceutical water production, purification, storage and distribution systems (stage II)

83. A subsequent two-week test period is used for further intensive monitoring of the pharmaceutical water production, purification, storage and distribution system, within which advanced SOPs are applied after successful completion of stage I. As a rule, the sampling procedure is normally the same as in stage I. The water for pharmaceutical use may be utilized for the production of medicinal products at this stage provided that the commissioning and test data obtained at stage I confirm the proper quality of the water for pharmaceutical use and subject to approval by the quality

assurance department (QA). Data obtained from tests conducted during stage II must confirm:

a) sustainability of the pharmaceutical water production, purification, storage and distribution system in the established ranges;

b) sustainability of production and distribution of water for pharmaceutical use of adequate quality and amount during operation of the system in accordance with the SOPs.

5. Confirmation of reliability and safety of pharmaceutical water production, purification, storage and distribution systems (stage III)

84. Usually, stage III lasts for 1 year from the date of successful completion of tests during stage II. At this stage, water for pharmaceutical use is utilized in production of medicinal products. The goals of this stage are:

a) confirmation of operation stability over a long period;

b) ensuring quality assessment of water for pharmaceutical use depending on seasonal changes.

85. The number of established points and the frequency of sampling, as well as the number of tests shall be reduced to the level established in accordance with the test results obtained during stages I and II.

6. Continuous monitoring of pharmaceutical water production, purification, storage and distribution systems

86. After the completion of stage III of the qualification program pharmaceutical water production, purification, storage and distribution systems, it is necessary to perform a review of the data collected, after which an ongoing monitoring plan is drawn up. Monitoring is carried out by conducting tests using the control devices incorporated into the pharmaceutical water production, purification, storage and distribution system (equipped with appropriately qualified warning systems). These control

devices should allow for monitoring of parameters such as flow rate, pressure, temperature, electrical conductivity and total organic carbon, as well as testing of physical, chemical and microbiological characteristics of the samples taken. Sampling shall be carried out from the points of consumption. In case that sampling from points of consumption is impossible, it is performed from the sampling points established when confirming reliability and safety of pharmaceutical water production, purification, storage and distribution systems. Sampling shall be carried out in accordance with the procedures established by the pharmaceutical manufacturer. The purging and drying procedures of pharmaceutical water production, purification, storage and distribution systems must also be established.

87. Tests are conducted in order to confirm compliance of the water for pharmaceutical use with requirements of pharmacopeial monographs of the Pharmacopoeia of the Union or the approved manufacturer's monograph. If necessary, they may include microbiological tests of the water quality. The data obtained in the course of monitoring are subject to trend analysis (typically the trend change values obtained must be within the tolerances of two sigmas (2σ)). Based on the previously described information, the permitted values for the levels of alarm and action are established. Any tendency towards frequent deviation from the permitted values of alarm levels entails the establishment of the main reason for such a deviation and subsequent corrective actions.

7. Maintenance of pharmaceutical water production, purification, storage and distribution systems

88. Pharmaceutical water production, purification, storage and distribution systems are operated in accordance with a controlled and documented maintenance program that includes:

a) specified maintenance intervals for the elements of pharmaceutical water production, purification, storage and distribution systems;

b) calibration program;

c) SOPs for each separate work with regard to pharmaceutical water production, purification, storage and distribution systems;

d) control of the approved spare parts;

e) development of a plan and instructions for cleaning the elements of pharmaceutical water production, purification, storage and distribution systems;

f) consideration and approval of activities to use pharmaceutical water production, purification, storage and distribution systems after completion of the work;

g) registration and analysis of possible problems and drawbacks when operating pharmaceutical water production, purification, storage and distribution systems.

8. Verification of pharmaceutical water production, purification, storage and distribution systems

89. Systems of production, purification, storage and distribution of water for pharmaceutical use (purified water in the form of unpackaged product, highly purified water in the form of unpackaged product and water for injection in the form of unpackaged product) are verified at appropriate intervals by representatives of the engineering services, quality assurance service, microbiologists, water production experts and experts in maintenance of pharmaceutical water production, purification, storage and distribution systems. During the verification, the following issues must be considered:

a) changes that occurred in the pharmaceutical water production, purification, storage and distribution system since the previous verification;

b) conditions and intensity of operation of the system;

c) reliability of operation of the system;

d) trends of the changes in the quality of the water for pharmaceutical use occurring in the system;

e) cases of system failure;

f) investigation of irregularities that occurred during the operation of the system since the previous verification;

g) the results of inconsistencies of the water for pharmaceutical use obtained with the specification requirements, obtained in the course of monitoring operation of the pharmaceutical water production, purification, storage and distribution system;

h) changes in the installation of the pharmaceutical water production, purification, storage and distribution system since the previous verification;

i) availability of updated documentation for the installation of pharmaceutical water production, purification, storage and distribution systems;

j) registration log books;

k) status of the current list of SOPs.

90. During operation of new systems or systems with regard to which operation unsafeness or instability have been discovered, it is also necessary to consider:

a) the need for conducting investigations in order to establish the causes of the identified or possible malfunctions;

b) corrective and preventive actions;

c) performance documentation on qualification of the pharmaceutical water production, purification, storage and distribution system in the form of design qualification (DQ), factory acceptance testing (FAT), installation qualification (IQ), site acceptance testing (SAT), operational qualification

(OQ), performance qualification (PQ)) or other documents related to the verification, as well as to the stages of monitoring the pharmaceutical water production, purification, storage and distribution system.

9. Inspection of pharmaceutical water production, purification, storage and distribution systems

91. Systems of production, purification, storage and distribution of water for pharmaceutical use (purified water in the form of unpackaged product, highly purified water in the form of unpackaged product and water for injection in the form of unpackaged product) are subject to periodic inspections by the authorized bodies of the Member States. Manufacturers of medicinal products should provide for conducting routine audit and self-inspection of the installed pharmaceutical water production, purification, storage and distribution systems.

92. Inspection of pharmaceutical water production, purification, storage and distribution systems is carried out in accordance with these Requirements and Rules. During inspection, the water production and the visible system of pipelines are inspected (including points of consumption) in order to establish that the pharmaceutical water production, purification, storage and distribution system has been properly designed, installed and is maintained (for example, that there are no leaks and that the pharmaceutical water production, purification, storage and distribution system corresponds to the diagram or drawing of pipelines and measuring instruments).

93. The program of inspection or audit of pharmaceutical water production, purification, storage and distribution systems includes:

a) checking the current drawing of the pharmaceutical water production, purification, storage and distribution system, containing all the system equipment (from feeding raw materials for obtaining water for pharmaceutical

use and up to points where the obtained water for pharmaceutical use is utilized, including sampling points and their designations);

b) checking the approved piping drawings (for example, in orthographic and/or isometric projection);

c) validation of the plan for sampling and monitoring operation of the pharmaceutical water production, purification, storage and distribution system, together with the drawing of all sampling points;

d) checking the training program on sample selection and testing;

e) checking the establishment of permitted controlled levels of alarm and action;

f) checking the results of monitoring operation of the pharmaceutical water production, purification, storage and distribution system, and also evaluating the revealed trends of changes in the quality of water for pharmaceutical use;

g) checking the last annual review of the pharmaceutical water production, purification, storage and distribution system;

h) consideration of all changes in the pharmaceutical water production, purification, storage and distribution system since the last audit of this system and checking the implementation of change control with regard to this system;

i) consideration of the registered deviations and their examination;

j) evaluation of the pharmaceutical water production, purification, storage and distribution system in terms of its current operational status and general condition;

k) checking maintenance, troubleshooting and repair log books;

l) checking calibration and verification of the most critical devices.