THE EURASIAN ECONOMIC COMMISSION
BOARD

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

May 10, 2018 **No. 6** Moscow

On the Quality Manual of Medicinal Herbal Preparations

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 to eliminate the differences in the quality requirements of herbal medicinal preparations,

recommends that the Member States of the Eurasian Economic Union, from the date of publication of this recommendation on the official website of the Eurasian Economic Union, apply the Quality Manual of herbal medicinal Preparations according to the Annex hereto, during pharmaceutical development, studies and registration of herbal preparations.

Chairman of the Eurasian Economic
Commission Board T. Sargsyan

ANNEX

to the Recommendation of the Board
of the Eurasian Economic Commission
No. 6 dated May 10, 2018

QUALITY MANUAL
of Herbal Medicinal Preparations

I. General provisions

1. This Manual provides rules for compilation of Module 3 of the registration dossier of herbal medicinal preparations 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 (hereinafter – the Rules).

2. This Manual describes the issues related to the quality of herbal medicinal preparations (including those containing vitamins and mineral components) in terms of their difference from the medicinal preparations containing only pharmaceutical substances with an established chemical structure. Preparations containing individual components or a mixture of components with clearly established chemical composition are not regarded as herbal medicinal preparations.

3. This Manual is inseparably associated with Annex No. 7 to 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. The consistent quality of herbal medicinal preparations can only be ensured if the raw materials are characterized strictly and in detail, with botanical identification of the herbal material used. In order

to ensure consistent quality of herbal medicinal preparations it is also necessary to know the geographical source and conditions under which herbal raw materials are procured. It is necessary to take into account the provisions of the Rules of good practices in growing, harvesting, processing and storing herbal raw materials, approved by the Decision of the Council of the Eurasian Economic Commission No. 15 dated January 26, 2018.

4. Herbal medicinal preparations may additionally contain vitamins or minerals. In this case, the quality of the herbal medicinal preparation, specifications and documentation for each vitamin and mineral component shall meet the requirements established by the acts included in the statutory power of the Eurasian Economic Union (hereinafter referred to as the Union) in the field of circulation of medicinal products.

5. The content of the registration dossier of a herbal medicinal preparation and all the necessary information must meet the requirements of the Rules.

II. Definitions

6. For the purposes of this Manual, the following terms shall be used, their meanings set forth in the respective definitions below:

«quantification (adduction)» is bringing the amount of the herbal preparation to a certain range of components merely by mixing different batches of herbal raw material and/or herbal preparations (for example, adducted extracts);

«components with known therapeutic activity» are substances or groups of substances, the chemical structure of which is established, and the contribution of which to the therapeutic activity of herbal raw materials (herbal pharmaceutical substance) or herbal medicinal preparation is known;

«drug extraction ratio» (DER) is the relation between the amount of the herbal raw material used for the production of a herbal pharmaceutical substance and the amount of the herbal pharmaceutical substance obtained, expressed as a number (actual range) in which the number before the colon indicates the relative amount of the herbal raw material, and the number after the colon indicates the relative amount of the herbal product obtained;

«acceptability criteria» are numerical limits, ranges, or other corresponding intervals for assessing test results;

«herbal medicinal preparations with a simplified registration dossier» are drugs for medical use meeting the conditions set out in Section 15.2 of Annex No. 1 to the Rules;

«herbal medicinal preparation» is a medicinal product that contains only herbal raw materials or herbal preparations as the active components;

«markers» are components or groups of components of a herbal raw material, herbal preparation or herbal medicinal preparation, the chemical composition of which is established, that are relevant for quality control, regardless of whether they possess or lack therapeutic activity;

«genuine (native) herbal preparation» is a herbal preparation that contains no excipients, even if, due to the technological constraints, such a herbal preparation is not available. Soft and liquid herbal preparations may contain a certain amount of solvent (extraction solvent);

«ratio of herbal substance to the genuine herbal preparation (DER genuine)» is the ratio of the amount of the herbal raw materials to the amount of the genuine herbal preparation obtained. The number (expressed as actual range) before the colon indicates the relative amount of herbal raw materials, and the number after the colon indicates the relative amount of the genuine herbal preparation obtained;

«herbal pharmaceutical substance (herbal preparation)» is the substance (product) obtained after processing herbal raw materials using methods such as extraction, distillation, pressing, fractionation, purification, concentration and fermentation. Such substances (products) include finely crushed herbal raw materials, tinctures, extracts, essential oils, pressed juices and processed exudates;

«specification» is the list of tests, references to analytical and biological techniques, as well as the relevant acceptance criteria (permissible limits), constituting numerical (quantitative) limits, ranges and other criteria for the tests described. A specification stipulates a set of criteria that must be met by herbal raw materials (herbal pharmaceutical substance (herbal preparation)) or a herbal medicinal preparation to be regarded as suitable for its intended purpose;

«standardization» means bringing the amount of the herbal raw materials, herbal pharmaceutical substance (herbal preparation) to a certain content of the component or group of components with known therapeutic activity either by adding excipients or by mixing batches of herbal raw materials and/or herbal preparations (for example, standardized extracts);

«extraction solvents» are solvents used in the extraction process.

For the purposes of this Manual, the concept of «herbal raw material» is used in the meaning as defined in the Rules of good practices in growing, harvesting, processing and storing raw materials of vegetable origin, the concept of «solvent» is used in the meaning as defined in the Manual for compilation of a regulatory quality document approved by the Eurasian Economic Commission (hereinafter the Commission).

III. Compilation of specifications for herbal medicinal preparations and instructions on presentation of qualitative and quantitative properties of active substances (active pharmaceutical ingredients) in them

7. Specifications are mandatory quality standards which are presented and justified by the manufacturer and approved by the authorized body of the Member State of the Union (hereinafter referred to as the Member State) as a condition for registration. Medicinal herbal raw material, herbal pharmaceutical substance (herbal preparation) and/or herbal medicinal preparation must conform to their specifications, i.e. the results of the tests of a herbal raw material, herbal pharmaceutical substance (herbal preparation) and/or herbal medicinal preparation conducted in accordance with the analytical and biological techniques described in the specifications must meet the specified acceptance criteria.

8. When preparing a specification, it must be taken into account that, depending on the production method, all herbal pharmaceutical substances (herbal preparations) are divided into the following types:

a) standardized – brought to a specified content of components with known therapeutic activity within the acceptance criteria (permissible limits). Standardization is achieved by adding excipients to the herbal pharmaceutical substances (herbal preparations) or mixing batches of herbal pharmaceutical substances (herbal preparations);

b) quantified (adducted) – brought to the content of components (active markers) in the specified range. Such adduction is achieved merely by mixing different batches of herbal raw materials and/or herbal preparations;

c) other – herbal pharmaceutical substances (herbal preparations), for which no components with known therapeutic activity or no active markers have been established.

9. Markers are used to calculate the amount of the herbal raw materials or herbal preparations in the finished herbal medicinal preparation, if the marker has already been quantified in the herbal raw materials or the herbal pharmaceutical substance (herbal preparation).

There are 2 categories of markers:

active markers are components or groups of components that typically contribute to the therapeutic activity;

analytical markers are components or groups of components which are used solely for analytical purposes.

10. If excipients are used in the production of active substances (e.g., for technical reasons or to standardize a herbal pharmaceutical substance (herbal preparation)), the specification must contain the name and amount of such excipients.

11. If there are monographs on the herbal raw material in the Pharmacopoeia of the Union or the pharmacopoeias of the Member States, its name is indicated in Russian and in Latin, and also in the official languages of the Member States. If necessary, generic and specific names are indicated in the name of the herbal raw material. In case that there are no monographs on the herbal raw material in the Pharmacopoeia of the Union or the pharmacopoeias of the Member States, its name should be indicated in Latin.

1. Whole herbal raw materials, shredded or powdered herbal pharmaceutical substances

12. For whole herbal raw materials, it is indicated in the specification that the raw materials are whole. For crushed or powdered herbal pharmaceutical substances (herbal preparations), the degree of crushing is

indicated. In addition, depending on the selected method of quantification, it is necessary to specify:

a) in case of standardization – the amount of the herbal pharmaceutical substance (herbal preparation) in the form of a range that corresponds to the specified amount of components with known therapeutic activity.

Example.

Active substance	
Name	*Amount*
Sennae folium (senna leaves)	*415-500 mg, which corresponds to 12.5 mg of hydroxyanthracene glycosides calculated as Sennoside B*

b) in case of quantification (adduction) – the amount of the herbal pharmaceutical substance (herbal preparation) in the form of a precise value, and the number of markers in the form of a range.

Example.

Active substance	
Name	*Amount*
Salix cortex (Willow bark)	*4 g, which corresponds to 40-48 mg of the total phenolic glycosides calculated as salicin*

c) in other cases – the amount of the herbal pharmaceutical substance (herbal preparation) in the form of a precise value.

Example.

Active substance	
Name	*Amount*
Althaeae officinalis radix (roots of common marshmallow)	*50 g*

2. Herbal pharmaceutical substances (herbal preparations) obtained by extraction of herbal raw materials

13. For herbal pharmaceutical substances (herbal preparations) obtained by method of extraction of herbal raw materials, the aggregate state of the extract, as well as the type and concentration of the solvent must be indicated in the specification. Besides, the following must be indicated:

a) for standardized extracts – the equivalent amount of the herbal raw materials (x-y) or ratio of the herbal raw materials to the genuine herbal product (DER or Der genuine) ((a-b):1). In this case, the amount of the genuine herbal product may be indicated in the form of a range corresponding to the specified amount of components with known therapeutic activity.

Example

Active substance

Name	*Amount*
Sennae folium (senna leaves) Dry extract (extraction solvent – ethanol 60% (volume per volume)) ((a-b): 1)	*50-65 mg, which corresponds to 12.5 mg of hydroxyanthracene glycosides calculated as Sennoside B*

or

Example

Active substance

Name	*Amount*
Sennae folium (senna leaves) Dry – extract (extraction solvent – ethanol 60% (volume per volume)) (equivalent to (x-y) senna leaves)	*50-65 mg, which corresponds to 12.5 mg of hydroxyanthracene glycosides calculated as Sennoside B*

b) for quantified (adducted) extracts – the equivalent amount of herbal raw material (x-y) or the ratio of the herbal raw materials to the genuine herbal product (DER or DER genuine) ((a-b): 1). The amount of the genuine herbal product must be indicated as a precise value, and the content of the quantified (adducted) herbal raw materials can be given as a range.

Example

Active substance

Name	*Amount*
Ginkgo biloba folia (maidenhair tree leaves) Dry extract (extraction solvent – 60% acetone (volume per volume)) ((a-b): 1)	*60 mg, which corresponds to 13.2-16.2 mg of flavonoids (calculated as flavone glycosides); 1.68-2.04 mg of ginkgolides A, B and C, and 1.56-1.92 mg of bilobalide*

Or

Example

Active substance

Name	*Amount*
Ginkgo biloba folia (maidenhair tree leaves) Dry extract (extraction solvent – acetone 60% (volume per volume)) (equivalent to (x-y) maidenhair tree leaves)	*60 mg, which corresponds to 13.2-16.2 mg of flavonoids (calculated as flavone glycosides); 1.68-2.04 mg of ginkgolides A, B and C, and 1.56-1.92 mg of bilobalide;*

c) for the remaining extracts – the equivalent amount of herbal raw material (x-y) or the ratio of the herbal raw materials to the genuine herbal product (DER or DER genuine) ((a-b): 1). In this case, the amount of the genuine herbal product must be indicated as a precise value.

Example

Active substance

Name	*Amount*
Althaeae officinalis radix (roots of common marshmallow) Dry extract (extraction solvent – ethanol 60% (volume per volume)) ((a-b):1)	*125 mg*

or

Active substance

Name	*Amount*
Althaeae officinalis radix (roots of	

common marshmallow) *125 mg*
Dry extract
(extraction solvent – ethanol 60%
(volume per volume))
(equivalent to (x-y) roots of common
marshmallow)

The values *a* and *b* or *x* and *y* must be justified by the results of the studies conducted by the applicant.

14. The composition of each extraction solvent or mixture of extraction solvents, as well as their aggregate state, must be specified. If, during the production of a herbal pharmaceutical substance (herbal preparation), any other substance is added to bring the content of components with known therapeutic activity to the specified value or with any other purpose, it should be specified as «other substance», and the genuine extract – as «active substance».

15. If, to bring the content of components with known therapeutic activity to the specified value or with any other purpose, different batches of the same extract are used, the final mixture must be regarded as the genuine extract and indicated as «active substance» in the composition. In this case, the complete information on the manufacturing process and quality control must be provided in the registration dossier of the herbal medicinal preparation.

IV. Description of the production process of the herbal medicinal preparation

16. In this Section, the production process means preparation of a herbal medicinal preparation from herbal raw materials and/or herbal pharmaceutical substances (herbal preparations). With regard to herbal medicinal preparations with a simplified registration dossier, the production process includes preparation of the herbal medicinal preparation from the herbal raw materials

and/or herbal pharmaceutical substances (herbal preparations), and/or vitamins and/or minerals.

17. The description of the production process must include detailed information on the specified process and measures to ensure quality control. The information on the production process must be provided in accordance with the guideline for the production of finished dosage forms determined by the Commission.

18. If the source material is a herbal pharmaceutical substance (herbal preparation), the description of its production and quality control must be presented in the «Management of raw materials» Section of Module 3 of the registration dossier of the herbal medicinal preparation.

19. Information on pharmaceutical development and validation of the production process must be provided in accordance with the Guideline on pharmaceutical development of medicinal products and the Guideline on validation of the production process of medicinal products determined by the Commission.

V. Quality control of raw materials

1. Quality control of herbal raw materials and herbal pharmaceutical substances

20. Quality control of herbal raw materials and herbal pharmaceutical substances (herbal preparations) must be conducted in accordance with the provisions of the Manual on selection of tests and acceptability criteria in specifications for herbal preparations, determined by the Commission.

Quality control of herbal raw materials

21. For each kind of a herbal raw material a complete specification must be provided. This requirement applies even if the applicant is not the manufacturer of the herbal raw material. If the source material is a herbal pharmaceutical substance (herbal preparation), such as fatty or essential oils used as active substances of herbal medicinal preparations, then, in the absence of other justification, it is necessary to submit a specification for the herbal raw material. The specification must indicate the scientific botanical name for the plant using the binominal nomenclature (genus, species, variety and author), chemotype (where necessary) and the part of the plant which is used.

22. In case there is no specific monograph on a particular type of herbal raw materials in the Pharmacopoeia of the Union or the pharmacopoeias of the Member States, it is necessary to submit the complete specification for this herbal raw material, which shall be drawn up similar to specific pharmacopoeial monographs on herbal raw materials in the Pharmacopoeia of the Union. When possible, the specification must include information on the habitat, harvest time of the herbal raw material, vegetation stage, treatment with pesticides during vegetation, etc., as well as on drying and storage conditions. The complete specification must be based on the latest scientific data.

For herbal raw materials containing components with known therapeutic activity, it is necessary to provide quantitative determination of the content of such components (along with the analytical techniques), which is specified in the form of a range, in order to ensure reproducibility of the quality of the herbal medicinal preparation. For a herbal raw material in which the components with known therapeutic activity have not been established, it is necessary to provide quantitative determination of markers (along with

analytical techniques). The choice of markers must be justified by the applicant.

23. According to a general rule, if the applicant has not submitted a justification for the use of alternative approaches, it is necessary to test the herbal raw material on microbiological purity, mycotoxins (aflatoxins, Ochratoxin A), residual pesticides, fumigants, toxic elements, potential contaminants, foreign substances, etc. The use of ethylene oxide for decontamination of the herbal raw material is not allowed. The specification must include a test for the content of radionuclides. You must submit the specifications and the description of analytical techniques, indicating the acceptability criteria. The analytical techniques not represented in the Pharmacopoeia of the Union must be validated in accordance with the guidance on validation of analytical techniques approved by the Commission. If validation of analytical techniques is not submitted, its absence shall be documented in the registration dossier of the herbal medicinal preparation.

24. For comparative testing (e.g. macroscopic study, chromatography, etc.) it is necessary to have standard samples of herbal raw materials.

Quality control of herbal pharmaceutical substances

25. If the herbal medicinal preparation has been obtained from a herbal pharmaceutical substance (herbal preparation), then along with a complete specification for the source herbal raw material it is necessary to provide a description and validation of the production process of the herbal pharmaceutical substance (herbal preparation), irrespective of whether the applicant is the manufacturer of the herbal pharmaceutical substance (herbal preparation). This information is allowed to be represented as part of the

registration dossier of the herbal medicinal preparation or according to the active substance master file procedure (see Annex No. 10 to the Rules).

26. If a specific pharmacopoeial monograph for the herbal pharmaceutical substance (herbal preparation) is included in the European Pharmacopoeia, the applicant may submit the certificate of conformity of the herbal pharmaceutical substance (herbal preparation) to the requirements of the European Pharmacopoeia, issued by the European Directorate for the quality of medicinal products and health care (if available).

27. For each herbal pharmaceutical substance (herbal preparation) a complete specification is required. The specification must be drawn up on the basis of the latest scientific data and must contain a detailed description of the product and data on authenticity and purity tests. Appropriate chromatographic methods must be used. The herbal pharmaceutical substance (herbal preparation) must be tested for microbiological purity, mycotoxins (aflatoxins, Ochratoxin A), residual pesticides, fumigants, toxic elements, as well as on the residual solvents content (if applicable), if it is connected with the results of previous analyses of the herbal raw material. The specification must include a test for the content of radionuclides. In addition, it is necessary to quantify the components with known therapeutic activity or markers. For a standardized product, the content of components with known therapeutic activity must be specified with the smallest possible deviation from the values obtained during pharmaceutical development (for both upper and lower limits).

28. The content of active markers used for quantified (adducted) extracts must be indicated in the form of a specified range.

29. With regard to extracts for which neither components with known therapeutic activity, nor active markers have been established, the minimum and the maximum content of the analytical marker, which is associated with

the validated analytical range as the basis for analytical validity within the framework of monitoring the quality of batches of these extracts, must be indicated. The analytical techniques must be described in detail.

30. If herbal pharmaceutical substances (herbal preparations) containing components with known therapeutic activity have been standardized (i.e. brought to a certain content of components with known therapeutic activity), the standardization method must be indicated.

31. If standardization is achieved by adding another substance, then its amount must be indicated in the form of acceptability criteria (permissible limits) or a range.

2. Quality control of vitamins and minerals

32. For vitamins and minerals that can be additionally introduced into the composition of herbal medicinal preparations with a simplified registration dossier, there should be a specification drawn up in accordance with the Manual on selection of tests and acceptability criteria in specifications for herbal preparations, determined by the Commission.

3. Quality control of excipients

33. Excipients, including those added during the production of herbal pharmaceutical substances (herbal preparations), must be described in accordance with the requirements to Module 3 of the registration dossier of the herbal medicinal preparations listed in Annex No. 1 to the Rules, including the need for conformity to pharmacopoeial monographs of the Pharmacopoeia of the Union or pharmacopoeias of the Member States. With regard to new excipients (excipients, not included in the Pharmacopoeia of the Union and the pharmacopoeias of the Member States), detailed information must be provided

just like for the active pharmaceutical substance (Section 3.2.S of Annex No. 1 to the Rules).

VI. Check tests at intermediate stages of the production process of a herbal medicinal preparation

34. A detailed description and the results of all tests must be provided, with the description of the analytical techniques and indication of the acceptability criteria (permissible limits) at each intermediate stage of the production process, if these tests cannot be conducted on the finished herbal medicinal preparation.

VII. Check tests of herbal medicinal preparations

35. Control tests of herbal medicinal preparations are carried out in accordance with the provisions of the Manual on selection of tests and acceptability criteria in specifications for herbal preparations.

36. The analytical techniques must be validated in accordance with the guidance on validation of analytical techniques.

37. The check tests of herbal medicinal preparations must ensure the possibility to determine qualitative and quantitative composition of the active substance (active substances). Specification must be submitted, which provides for the use of markers, if no components with known therapeutic activity have been established in the composition of the herbal medicinal preparation. The components with known therapeutic activity included in the composition of the herbal pharmaceutical substance (herbal preparation) must be included in the specification and quantified. For herbal medicinal preparations with a simplified registration dossier, which contain vitamins

and/or minerals, the specification must include the name of the vitamins and/or minerals, and their content must be indicated.

38. If the herbal medicinal preparation contains a combination of several types of herbal pharmaceutical substances (herbal preparations) and it is not possible to determine the content of each active substance, then cumulative quantification of multiple active ingredients is allowed. The need for such a method of quantification must be justified by the applicant.

39. In case the applicant has not submitted any other justifications, then to confirm microbiological purity of a herbal raw material, herbal pharmaceutical substances (herbal preparations), it is necessary to be guided by the criteria stipulated in the Pharmacopoeia of the Union, and in their absence – in the pharmacopoeias of the Member States. The frequency of studies must be justified by the applicant.

VIII. Stability studies of herbal pharmaceutical substances and herbal medicinal products

40. The Section on stability studies within the registration dossier of the herbal medicinal preparation must be in accordance with the requirements to stability studies of pharmaceutical substances and medicinal products, approved by the Commission.

41. Since a herbal pharmaceutical substance (herbal preparation) is generally regarded as the active ingredient, to simply determine stability of components with known therapeutic activity is insufficient. To the extent possible, stability of other substances present in the herbal pharmaceutical substance (herbal preparation) must be confirmed, for example, by using the corresponding characteristic chromatograms (the «fingerprint» method). It is

also necessary to confirm that their relative content remains comparable to the original characteristic chromatogram.

42. If a herbal medicinal preparation contains a combination of several types of herbal pharmaceutical substances (herbal preparations), and it appears impossible to determine the stability of each active ingredient, the stability of the herbal medicinal preparation must be established using the corresponding characteristic chromatograms, appropriate methods of cumulative quantification, physical, organoleptic and other appropriate tests. The adequacy of stability tests within the registration dossier must be justified by the applicant.

43. For medicinal products containing a herbal pharmaceutical substance (herbal preparation) with components with known therapeutic activity, the deviation of the content of these components throughout the proposed shelf life should not exceed ±5% of the declared quantified value, unless the applicant submits a justification for the possibility of using other acceptance criteria (permissible limits). For medicinal products containing a herbal pharmaceutical substance (herbal preparation) for which no components with known therapeutic activity have been established, an acceptable deviation of the content of the marker throughout the proposed shelf life is ±10% of the initial value, unless the applicant submits a justification for the possibility of using other values of acceptance criteria (permissible limits).

44. For herbal medicinal preparations with a simplified registration dossier, containing vitamins and/or minerals, it is necessary to confirm stability of the vitamins and/or minerals.