ANNEX

to Recommendation of the Board
of the Eurasian Economic Commission
no. of 20

Guideline on specifications: Selection of Tests and Acceptance Criteria for Herbal Medicinal Products

I. General Provisions

1. This Guideline contains general principles for the compilation and justification of specifications for herbal substances (herbal preparation) and herbal medicinal products for their registration in accordance with the Rules for Registration and Examination of Medicinal Products for Human Use, as approved by Decision of the Council of the Eurasian Economic Commission no.78 of November 3, 2016 (hereinafter referred to as «the Rules»).

2. This Guideline is inextricably linked with the Guideline on Quality of herbal medicinal products, as approved by the Eurasian Economic Commission (hereinafter referred to as «the Commission»).

3. With regard to herbal medicinal products of traditional application, a simplified registration procedure was introduced in accordance with Section 15.2 of Annex 1 to the Rules. The quality of a herbal medicinal product is not guaranteed by its long-term traditional application, therefore, all general principles of quality assurance are also applicable to traditional herbal medicinal products.

4. Traditional herbal medicinal products may additionally contain vitamins and (or) minerals. For such products, specific guidance is given in this Guideline for mixtures of herbal substances (herbal preparations) with vitamins and (or) minerals. In addition, the quality, specifications and

documentation for each vitamin and mineral must comply with the documents and regulations included in the Union law.

5. A specification is a list of tests, references to analytical and biological methods, as well as relevant acceptance criteria (permissible norms), representing numerical (quantitative) limits, ranges and other criteria for the tests described. A specification provides with a set of criteria that a herbal substance (herbal preparation) or a herbal medicinal product must correspond to in order to be considered suitable for its intended use. «Compliance with the specification» means that a herbal substance (herbal preparation) and (or) a herbal medicinal product meet the acceptance criteria set in the specification if they stand the tests using the analytical methods established in the registration dossier.

6. Specifications are mandatory quality standards that are proposed and justified by the manufacturer and approved by the authorized body as registration conditions.

7. The specifications are a part of the overall strategy for the quality control of herbal substances (herbal preparation) and herbal medicinal products, which is aimed at ensuring the quality and consistency of the properties of the medicinal plant products. Other elements of this strategy are as follows:

establishment of characteristics on the basis of which the specifications are made, during the development of the product;

compliance with the Rules of Good Manufacturing Practices of the Eurasian Economic Union, as approved by Decision of the Council of the Eurasian Economic Commission no. 77 of November 3, of 2016 (hereinafter referred to as «the Rules of Good Manufacturing Practice») and good practices for the cultivation, collection, processing and storage of plant raw

materials approved by the Commission;

validated production process, for example, testing of raw materials;

internal control, stability testing, etc.

8. In the case of herbal medicinal products, specifications are usually made for the herbal substance, herbal preparation and herbal medicinal product itself. The specifications are intended primarily to determine the quality of the medicinal plant material (herbal preparation) or herbal medicinal products, and not to establish their full characteristics and shall focus on quality indicators that confirm safety and efficacy.

9. The quality of herbal substances, herbal preparations and herbal medicinal products is determined by the quality of the plant raw material, development, internal control, compliance with the Rules of Good Manufacturing Practices and the validation of the manufacturing process, as well as the specifications applied to herbal substances, herbal preparations and herbal medicinal products during the process of their development and production.

10. This Guideline reviews specifications, that is, their components such as tests, analytical methods and acceptance criteria used to ensure the quality of herbal substances (herbal preparations) and herbal medicinal products at the time of release and during the shelf life. Specifications are an important, but not the only, component of quality assurance. To ensure the continuous production of herbal substances (herbal preparations) and herbal medicinal products of high quality, all the above provisions must be taken into account.

11. The provisions of this Guideline are applicable to herbal medicinal products at the registration stage or already registered ones.

12. The provisions of this Guideline are not applied to herbal substances (herbal preparations) and herbal medicinal products at the stage of clinical

development, but they shall be taken into account for subsequent registration.

13. This Guideline provides recommendations on the acceptance criteria that must be developed for all herbal substances (all herbal preparations) and herbal medicinal products, i.e. universal acceptance criteria, as well as special criteria for individual herbal substances (herbal preparations) and (or) finished dosage forms of herbal medicinal products.

14. This Guideline reflects advanced achievements at the time of writing, but it is not exhaustive document. New analytical methods and modifications of existing methods are constantly emerging. With sufficient justification, they shall also be used.

15. The provisions in this Guideline shall be taken into account when developing and justifying the specifications. They are not universal, but each of them must be considered in certain circumstances.

16. This Guideline contains provisions in the form of a brief description of the cases when it may be applicable. Generally, detailed approaches and proposals for the implementation of these provisions shall be justified by the applicant and approved by the appropriate authorized body (expert organization) before they are put into effect.

II. Terms and Definitions

17. For the purposes of this Guideline, the terms below shall have the following meanings:

«Quantification» means a method of bringing a herbal preparation to a clearly defined component composition solely by mixing different batches of herbal substances and (or) herbal preparations (for example, reduced extracts);

«Constituents with known therapeutic activity» mean substances or a

group of substances whose chemical composition is established and whose contribution to the therapeutic activity of a herbal substance, herbal preparation or herbal medicinal product is known;

«Acceptance criteria» mean numerical limits, ranges or other appropriate intervals for the evaluation of test results;

«Herbal substances» mean fresh or dried plants, algae, fungi or lichens or parts thereof, whole or crushed, used for the manufacture of medicinal products. Some exudates (for example, gum-arabic, gums), not subjected to special treatment, are also considered as herbal substances. herbal substances are precisely determined by the part of the plant used and botanical name in accordance with the binominal system (genus, species, subspecies and author);

«Herbal medicinal products» mean medicinal products containing as active ingredients exclusively herbal substances and (or) products based on them;

«Traditional herbal medicinal products» mean medicinal products for human use, which meet the conditions set out in section 15.2 of Annex 1 to the Regulations;

«Markers» mean components or groups of components of herbal substances, herbal preparation or herbal medicinal products, the chemical composition of which is determined to be of interest from the viewpoint of quality control, regardless of whether they have therapeutic activity. Markers serve to calculate the amount of herbal substances, herbal preparation in the finished medicinal product, if the marker has already been quantified in herbal substance or in a herbal preparation;

There are two categories of markers:

Active markers are components or groups of components that, as a

general rule, contribute to the therapeutic activity.

Analytical markers are components or groups of components that serve exclusively for analytical purposes;

«Genuine (native) herbal preparation» means a herbal preparation without auxiliary substances, even if for technological reasons such a product is not available. At the same time, soft and liquid herbal preparations may contain a certain amount of solvent (extraction solvent);

«Degradation product» means any impurity resulting from the chemical conversion of the active substance during the process and (or) storage by exposure to light, heat, pH, water, reaction with an auxiliary substance or primary packaging. Due to the specific nature of plants for herbal substances, herbal preparations or finished medicinal products, it is usually necessary to specify in the specification only those degradation products that play an important toxicological role;

«Herbal preparations» mean substances (products) obtained as a result of the treatment of plant raw materials by methods such as extraction, distillation, spinning, fractionation, purification, concentration, and fermentation. Such products include finely divided or powdered plant raw materials, tinctures, extracts, essential oils, squeezed juices and processed exudates;

«Herbal teas» (fresh herbal teas) mean freshly prepared aqueous extracts from one or more herbal medicinal raw materials obtained by brewing, infusion or soaking. Herbal teas, as a rule, are delivered in bulk form or packaged in sachets;

«Specification» means a list of quality indicators, references to analytical methods and tests and norms that represent numerical (quantitative) limits, ranges and other criteria for these quality indicators. The

specification indicates a set of criteria that a herbal substance (herbal preparation) and (or) a herbal medicinal product must correspond to in order to be considered suitable for its intended use. It is considered that the material or products meet the requirements of the specification, if it meets the specified acceptance criteria when tested according to accepted test procedures;

«Specific tests» mean tests applied to a specific medicinal plant material (herbal preparation) or a specific herbal medicinal product, depending on their specific properties and (or) purpose;

«Standardization» means a method of bringing a herbal raw material herbal preparation) to a clearly defined composition of a component or group of components with known therapeutic activity by the addition of auxiliary substances or by mixing a series of medicinal plant materials and (or) herbal preparations (for example, standardized extracts);

«Universal tests» mean tests potentially applicable to all herbal substances (herbal preparations) or to all herbal medicinal products, for example, description, authenticity, quantitation and impurity testing;

«Extraction solvents» mean solvents used in the extraction process.

III. Guidance on the selection of tests and criteria in specifications for herbal medicinal products

1. Characteristics

18. The consistency of the quality of plant products can only be guaranteed if the composition of herbal substances is specified. Therefore, providing characteristics of herbal substances (herbal preparations) or herbal medicinal products, which includes a detailed analysis of the morphological and phytochemical properties of plants and a detailed description of the production process of herbal medicinal products, is a prerequisite for the

development of complete and valid specifications.

19. Acceptance criteria shall first of all be established and justified on the basis of information from the series used for preclinical (clinical) studies or on the basis of information from relevant literature sources. However, other data on the series (used for production validation, stability studies), as well as for the series produced earlier, shall be taken into account.

20. Detailed definition of characteristics is usually performed only at the development stages and, if necessary, at the stage of significant changes in the technological process. If necessary, at the time of submission of documents for registration, the manufacturer must have their own appropriate standard samples (primary and production) for determining the authenticity and quantification of the components of the production series.

Macroscopic (microscopic) characteristic

21. Macroscopic (microscopic) characteristics shall include characteristic properties (attributes), which make it possible to distinguish herbal substances from potential impurities (surrogates).

Phytochemical characteristic

22. Phytochemical characteristics include analytical data on the components of the composition, including components with known therapeutic activity and compounds suitable for use as active markers or analytical markers. Phytochemical characteristics include a characteristic chromatogram - a method of «fingerprints».

Impurities

23. Impurities can be classified as follows:

impurities associated with the starting material (active substances, auxiliary substances) and packaging materials;

technological impurities generated as a result of the production process.

24. In addition, for herbal medicinal products, as far as possible, the following groups of impurities shall be considered:

contaminants, which include toxic metals, pesticide and fumigant residues, mycotoxins (aflatoxins, ochratoxin A), and microbiological contamination, including those originating from external sources, radionuclides;

products of decomposition formed during the decomposition of herbal substances (herbal preparations). Due to the specific nature of herbal medicinal products, those decomposition products that are toxic (have a toxicological effect) shall be indicated first;

residual solvents, the appearance of which is associated with their use in the manufacturing process.

Biological variability

25. It includes the use of historical data related to production series and literature data on biological variability to justify the specification.

2. Principles of development and compilation

26. The basis for setting requirements to specifications shall be the experience and data accumulated in the development of a herbal medicinal product. In general, it is only necessary to check the herbal medicinal product for compliance with those quality characteristics that are uniquely associated with a particular dosage form, a herbal substance or a herbal preparation. On this basis, it is possible to exclude or replace certain tests. For example:

a reduced volume of tests for pesticide residues in the event that only organic fertilizers without pesticides are used for the cultivation of herbal substances, etc., and the absence of potential contamination from neighbouring plantations is proved;

exclusion or reduction of tests for the microbiological purity of such herbal preparations as extracts or tinctures with a high content of ethyl alcohol, if it is confirmed by scientific data (guidance on microbiological indices of herbal medicinal products approved by the Commission).

3. Pharmacopoeia methods and acceptance criteria

27. Tests and acceptance criteria contained in the Pharmacopoeia of the Union shall be applied, and in the absence of it, in the pharmacopoeias of the Member States of the Union.

4. Periodic (sample) tests

28. Periodic or sample tests mean certain tests on pre-selected series when released and (or) at predetermined intervals. For example, this approach may be applicable to dissolution tests, residual solvents and microbiological tests for solid dosage forms (Annex 2 to the Guideline on the Preparation of a Regulatory Document on the Quality of a Medicinal Product, as approved by the Commission). Sometimes this approach can be implemented after registration of a herbal medicinal product in accordance with the Rules of Good Manufacturing Practice and approval by the authorized body (expert organization).

5. Criteria for the acceptability of quality indicators at the time of production and for a specified shelf life

29. As regards herbal medicinal products, the approach is to establish

various criteria for the acceptability of quality indicators in the specification at the time of production, in comparison with the specification for a specified shelf life. In exceptional cases, this approach can be used for herbal substances and herbal preparations, if this is justified. The approach is to establish more stringent criteria for quality indicators in the specification at the time of production than in the specification applicable during the specified shelf life. This can be used to quantify and determine the level of impurities (decomposition products).

6. Tests during the production process

30. Tests during production are tests that can be carried out during the production of a herbal preparation or a herbal medicinal product; they do not include tests performed before the release of a series of products.

31. In-process tests conducted to adjust process parameters within the operating range (e.g. hardness and abrasion control of tablets, which will be coated) are not included in the specification.

32. Some tests conducted during the manufacturing process (for example, solution pH determination) can be used to confirm compliance with the specifications for the finished product, provided that this test is included in the specification and the criteria for its acceptability are similar or more stringent.

7. Alternative methods

33. Alternative methods are test methods that can be used to measure (determine) any indicator and provide quality control of herbal substances (herbal preparations) or herbal medicinal products in the same or to a greater extent than official methods. For example, for tablets, if it is confirmed that

the level of decomposition products does not increase during the manufacturing process, it is permissible to use the spectrophotometric method for the output control instead of the officially adopted chromatographic test method. However, to confirm compliance with the acceptance criteria, the chromatographic method shall continue to be used for the prescribed shelf-life of the preparation.

8. Modern methods

34. The existing analytical methods are continuously improved, and new analytical methods are being developed. It is necessary to introduce new modern analytical methods if their use provides additional quality assurance or it is justified by other reasons.

9. Standard sample

35. A standard sample or standard material is intended to be used as a standard in the authenticity test or the impurity test. For a herbal medicinal product, a standard sample can be:

herbarium specimen of a herbal substance;

a sample of herbal preparation (extract or tincture);

a substance with a known chemical composition, for example, a component with known pharmacological efficacy;

active or analytical marker;

known impurity.

36. The quality of the standard sample must correspond to its purpose. It is necessary to control the composition of standard samples of herbal substances and herbal preparations intended for quantitative testing, and their purity shall be determined only with the help of validated analytical methods.

Herbarium specimens

37. In the case herbal substances are not described in the Pharmacopoeia of the Union and in the pharmacopoeia of Member States, it is necessary to have a herbarium sample of a plant or a part thereof (for example, if the plant is a tree, etc.).

10. Statistical analysis

38. The quantitative test data provided in the report shall be accompanied, if necessary, by appropriate statistical analysis.

39. The methods of statistical analysis, including their justification and confirmation, must be fully described. The description shall be sufficiently clear to enable an independent calculation of the results presented.

IV. Specifications: definition and justification

1. Specification definition

40. A specification is defined as a list of tests, references to analytical and biological methods, as well as relevant acceptance criteria (permissible norms), representing numerical (quantitative) limits, ranges and other criteria for the tests described. A specification provides with a set of criteria that a herbal substance (herbal preparation) and (or) a herbal medicinal product must correspond to in order to be considered suitable for its intended use. «Compliance with the specification» means that a herbal substance (herbal preparation) and (or) the herbal medicinal product meet the acceptance criteria set in the specification if they stand the tests using prescribed analytical methods.

41. Specifications are mandatory quality standards that are proposed and justified by the manufacturer and approved by the authorized body.

42. In addition to testing finished products, specifications may include inter-operational and periodical (sampling) tests. In such cases, the specification shall indicate which tests are conducted routinely and periodically.

43. Herbal substances (herbal preparation) and (or) herbal medicinal product must meet the acceptance criteria.

44. It shall be noted that making changes to the specifications after approval of the application will require prior approval of the authorized body (expert organization).

Justification of specifications

45. The development of specifications for herbal substance (herbal preparation) and (or) herbal medicinal product is a part of the overall quality management strategy, which includes:

control of raw materials and auxiliary substances;

control in the production process;

validation;

stability tests;

control of the series homogeneity.

Together, these elements guarantee the maintenance of the proper quality of herbal substance (herbal preparation) and (or) herbal medicinal product.

46. Since the purpose of the specification is the confirmation of the quality of the herbal medicinal product, and not of the specific characteristics of the herbal medicinal product, the manufacturer shall provide a rationale for including and (or) excluding specific quality indicators from the specification.

47. The following paragraphs shall be taken into account when

establishing scientifically based specifications.

2. Specifications for herbal substances

48. Specifications for herbal substances shall include:

botanical characteristics of the medicinal plant (part of the plant) (genus, species, variety, chemotype, use of genetically modified organisms);

macro and microscopic characteristics, phytochemical characteristics (authenticity, quantitative determination, limit test for components with known therapeutic activity, markers, toxic components);

data on biological (geographic) variability;

description of the conditions of cultivation, collection, drying (microbiological contamination, aflatoxins, toxic elements, radionuclides, etc.);

data on chemical treatment before and after collection (pesticides, fumigants);

description of the profile and stability of components.

Specifications for herbal preparations

49. Specifications for herbal preparations shall include:

requirements to the quality of herbal substances;

information on a herbal preparation (the ratio of the feedstock to the extract obtained, the content of the extraction solvent (solvents));

description of the method of preparation of a herbal preparation;

list of components of the composition, that is the components with known therapeutic activity, active (analytical) markers, other components of the composition (authenticity, quantitation, and limit testing);

drying conditions (for example, microbiological contamination, residual solvents in extracts, etc.);

profile and stability of the components of the composition;

microbiological purity during storage;

series involved in preclinical (clinical) trials (safety assessment and evaluation of efficacy), if applicable.

Specifications for finished herbal medicinal products

50. Specifications for finished herbal medicinal products shall include:

data on the quality of herbal substances and (or) herbal preparations;

description of the process (temperature effect, residual solvents, etc.);

profile and stability of active components (composition) during packaging;

series involved in preclinical (clinical) trials (safety assessment and evaluation of efficacy), if applicable.

51. The specification shall be based on development data (preclinical, clinical trials, stability tests, validation tests), literature sources and data on previously produced series (if available).

52. Specifications shall be developed taking into account the technological processes, especially in the presence of products of decomposition (impurities) of the components of the medicinal product and technological impurities. The change in the process and the decomposition products that are formed during storage can lead to the fact that the products will differ from the series involved in preclinical (clinical) tests. The significance of such changes needs to be assessed.

53. Given the complex composition of herbal medicinal products, it cannot be assumed that there is a single method of quantitative determination (an indicator for control) of the stability of a herbal substance (herbal preparation) and herbal medicinal product. Therefore, the applicant shall offer

a number of specific tests and stability tests, by which it is possible to determine the changes in the quality of the medicinal product during the whole shelf life.

54. The list of included trials depends on the specific medicinal product.

55. Applicants must comply with the requirements to the study of the stability of herbal preparations, which have been approved by the Commission.

3. Universal tests and acceptance criteria

56. When developing projects of universal (general) tests and acceptance criteria, the recommendations of the validation Guideline for analytical methods approved by the Commission shall be followed.

Herbal substances

57. Herbal substances represent a diverse spectrum of both the whole plant and its parts, including leaves, grass, roots, flowers, seeds, bark, etc. A comprehensive specification shall be developed for each type of herbal substances, even if a herbal preparation is an original material for the production of a herbal medicinal product.

58. If the active substances in the herbal medicinal product are fatty or essential oils, a specification for herbal substances is required (in the absence of other justifications).

59. A specification is developed on the basis of the latest scientific data and presented in the same way as in the monographs of the Pharmacopoeia of the Union, and in the absence of it - in monographs of the pharmacopoeias of the Member States.

60. The following tests and acceptance criteria are applicable to all types

of herbal substances in general:

a) the qualitative characteristics of the botanical source, the part of the plant used and its condition (the whole plant, its part, powdery, fresh, dry), geographical source (sources) and conditions for obtaining medicinal plant material;

b) characteristic features - a qualitative characteristic of organoleptic properties with indications of distinctive features, macro and microscopic botanical features of medicinal plant material;

c) authenticity - authenticity tests shall provide an opportunity to distinguish related species and (or) to identify the possible presence of unwanted impurities (surrogates). Trials of the authenticity of herbal substances must be specific; they usually include a combination of three or more tests: macroscopic signs, microscopic signs, chromatographic methods, chemical reactions;

d) tests:

foreign inclusions; common ash;

ashes insoluble in hydrochloric acid;

extractives soluble in water;

extractive substances;

particle size - in some cases for herbal substance intended for the production of herbal teas or solid herbal medicinal products, the particle size may have a significant effect on dissolution rate, biological availability and (or) stability. In such cases, the determination of the dispersed composition (particle size distribution) of the herbal substances shall be carried out using the appropriate method, and acceptance criteria shall be determined. The particle size can also influence the disintegration time of the solid dosage forms;

moisture content - if the herbal substances are hygroscopic, then this test must be included in the specification. Data on the effect of moisture absorption shall serve as justification of the acceptability criteria. For plant raw materials not described in the Pharmacopoeia of the Union and in the pharmacopoeias of the Member States, the acceptance criteria shall be justified taking into account the data on moisture absorption. Acceptable methods of determination are «Loss in mass during drying» or a specific method for determining the moisture content (for plants containing essential oils);

impurities - inorganic impurities, toxic (heavy) metals. The necessity to include tests and determine the acceptance criteria for inorganic impurities shall be studied during development and is based on the species specificity of the plant, its growing conditions and the production process conditions. In determining the criteria for acceptability, safety must first be followed. Where reasonably justified, the methodologies and acceptance criteria for the indicator «sulphated ash (residue after ignition)» shall follow the requirements of the Pharmacopoeia of the Union, and in the absence of it - the requirements of the pharmacopoeias of Member States;

microbiological purity - it is recommended to indicate the total number of aerobic microorganisms, the total amount of yeast and mold fungi, and the absence of specific microorganisms. When considering the inclusion of other possible pathogens (e.g. *Campylobacter and Listeria* species), the source of herbal substances in addition to those indicated in the Pharmacopoeia of the Union, and in the absence in it - in the pharmacopoeias of the Member States, shall be considered. Determination of microbiological purity is carried out using pharmacopoeial or other validated methods. Recommendations on acceptance criteria are given in the Pharmacopoeia of the Union and, in the

absence of it, in the pharmacopoeias of Member States;

mycotoxins (aflatoxins, ochratoxin A) - the possibility of contamination with mycotoxins shall be considered. To monitor the content of mycotoxins, appropriate validated methods shall be used and the acceptance criteria established;

pesticides, fumigants - it is necessary to consider in detail the potential for the presence of residues of pesticides, fumigants, etc. If necessary, appropriate validation methods shall be used to check the content of possible residues and justify the acceptance criteria;

radioactivity - all herbal substances shall be checked for radionuclides;

Other tests (e.g. swelling ratio).

Quantitation

61. For herbal substances which contain components with known therapeutic activity or active markers, a detailed methodology for their quantitative determination is necessary. If possible, a specific method of quantitative determination shall be included in the specification to control the stability of herbal substances.

62. In cases where the use of a non-specific method of quantification is justified, other auxiliary test procedures may be used to achieve full specificity.

63. For herbal substances, in relation to which there is no information on the constituent components responsible for the therapeutic activity, it is necessary to quantify active (analytical) markers. Reasons for choosing markers shall be justified. For example, the rationale may be a reference to the method of quantifying the marker in the corresponding monograph of the Pharmacopoeia of the Union and, in the absence of it, in the relevant monographs of the pharmacopoeias of the Member States.

Herbal preparations

64. Herbal preparations are diverse in nature: from simple, crushed materials to extracts, tinctures, oils and resins. For each herbal preparation, a detailed and complete specification must be developed.

65. The following tests and acceptance criteria are applicable to all herbal preparations in general:

a) definition - information on botanical origin and type of product (dry, liquid extract, etc.); the ratio of herbal substance in the product;

b) characteristic features - a qualitative characteristic of organoleptic properties;

c) authenticity - authenticity tests must provide the ability to distinguish between surrogates (undesirable impurities) and be specific to the test product. Confirmation of authenticity solely on the basis of retention time in a chromatographic test is not considered a specific one. A combination of chromatographic tests (for example, HPLC and TLC) or a combination of different tests in a single procedure, for example, HPLC / UV, HPLC / MS or GC / MS, is considered acceptable;

d) tests:

Moisture content (for hygroscopic products) - the procedure for «Loss in mass during drying» may be acceptable for testing, however, in some cases (for products containing essential oils), a specific method for determining the moisture content is required. Data on the effect of moisture absorption shall serve as justification of the acceptability criteria.

Impurities are residual solvents (in accordance with the requirements set forth in the Pharmacopoeia of the Union and, in the absence thereof, with the requirements set forth in the pharmacopoeias of the Member States); inorganic impurities, heavy (toxic) metals - the necessity to incorporate the tests and

determine the acceptance criteria for inorganic impurities shall be studied during development and is based on the species specificity of the plant, its cultivation and production process. It shall be possible to concentrate toxic residues in the production process. If the technological process allows reducing the content of toxic residues, it is sufficient to conduct tests only on herbal substances. Ultimately, safety requirements shall be a basis of the established acceptance criteria. Where this is justified, methods and criteria of acceptability for indicators «sulphate ash (residue after ignition)», «heavy metals» must meet the requirements of the Pharmacopoeia of the Union and, in the absence of it, the requirements of the pharmacopoeias of the Member States;

microbiological purity - the total number of aerobic microorganisms, the total amount of yeast and mold fungi, and the absence of specific microorganisms shall be indicated. Determination of microbiological purity is carried out using pharmacopoeial or other validated methods. Recommendations on acceptance criteria are given in the Pharmacopoeia of the Union and, in the absence of it, in the pharmacopoeias of Member States;

mycotoxins (aflatoxins, ochratoxin A) - the possibility of contamination with mycotoxins shall be considered. To monitor the content of mycotoxins, appropriate validated methods shall be used and the acceptance criteria established;

pesticides, fumigants, etc. - it is necessary to consider in detail the potential for the presence of residues of pesticides, fumigants, etc., taking into account the analysis of the original herbal substance. If necessary, appropriate validated methods shall be used to check the content of possible residues and justify the acceptance criteria.

e) quantitative determination - for herbal preparations that contain

components with known therapeutic activity or active markers, a detailed description of the quantification method is required. If possible, a specific method of quantitative determination shall be included in the specification to control the stability of a herbal preparation. If the use of a non-specific method of quantification is justified, other auxiliary analytical methods may be used to achieve full specificity. For example, the quantitative determination of anthraglycosides by a spectrophotometric method can be supplemented with a specific authenticity test (characteristic chromatogram - the «fingerprint» method). For herbal preparations for which there is no information on the components responsible for their therapeutic activity or active markers, it is necessary to quantify analytical markers or to perform other validated tests. Reasons for choosing markers shall be justified.

Vitamins and minerals in herbal medicinal products

66. To herbal medicinal products for human use, which contain vitamins and (or) minerals as auxiliary substances, in general, the following tests and acceptance criteria are applicable:

a) authenticity - tests shall establish the authenticity of vitamins and (or) minerals;

b) quantitative determination - validated methods of quantification of vitamins and (or) minerals are required;

c) impurities - control of the impurity content shall be carried out in accordance with the rules for studying impurities in medicines and setting requirements for them in specifications approved by the Commission, articles of the Union Pharmacopoeia on residual solvents, and in the absence thereof - by articles in the pharmacopoeias of Member States on residual solvents. It is necessary to monitor the impurities that form when decomposing vitamins or

minerals. If a significant amount of data obtained using appropriate analytical methods demonstrating that vitamin (vitamins) and (or) minerals are not decomposed in this particular formulation and under specific storage conditions is presented, tests for determining the content of degradation products can be reduced or eliminated (with approval of the authorized body (expert organization)).

Herbal medicinal products

67. The following tests and acceptance criteria are applicable to all types of herbal medicinal products in general:

a) description - a description of the quality characteristics of the dosage form (e.g. size, shape, colour). Acceptance criteria shall include the appearance at the end of the shelf life. If the colour changes during storage, it is advisable to conduct quantitative tests;

b) authenticity - the tests shall be specific for the herbal substances (herbal preparation) that make up the finished medicinal product and enable to distinguish between surrogates (undesirable impurities). Confirmation of authenticity solely on the basis of retention time in a chromatographic test is not considered a specific one. A combination of chromatographic tests (for example, HPLC and TLC) or a combination of different tests in a single procedure, for example, HPLC / UV, HPLC / MS or GC / MS, is considered acceptable. To confirm the authenticity of herbal medicinal products containing powdered or ground herbal substances, a micro- and macroscopic characteristic shall be used in combination with other methods;

c) quantitative determination - for herbal medicinal products containing herbal substances and (or) herbal preparations containing components with known therapeutic activity, validated and detailed methods of quantitative

determination of these components are necessary. If possible, to control the stability of herbal substance and (or) a herbal preparation, a specific test method shall be included in the specification of the herbal medicinal product. In cases where the use of a non-specific method of quantification is justified, other auxiliary analytical methods may be used to achieve full specificity. For example, the quantitative determination of anthraglycosides by a spectrophotometric method can be supplemented with a specific authenticity test (characteristic chromatogram - the «fingerprint» method). If the herbal medicinal product contains herbal substances and (or) herbal preparations for which there is no information on the components responsible for their therapeutic activity, it is necessary to quantify active or analytical markers or conduct other validated tests. Reasons for choosing markers shall be justified. In those cases where it is not possible to make a quantitative determination of each type of herbal substance in a herbal medicinal product, other reasonable methods of determination are required (for example, in the case of multicomponent herbal medicinal products for human use, the same markers may be present in several types of a herbal preparations);

d) impurities - control for the content of impurities shall be carried out in accordance with the rules for the study of impurities in medicinal products and the establishment of requirements to them in specifications, as approved by the Commission, the Union Pharmacopoeia, and, in the absence of such, - by the pharmacopoeias of Member States. It is not necessary to conduct tests in the herbal medicinal product of those impurities that have already been controlled during the testing of herbal substances (herbal preparations) (for example, residues of pesticides (fumigants), heavy metals). Similarly, there is no need to control the residual solvents that appear during the production of a herbal medicinal product (for example, during extraction), if their content is

controlled during production. However, it is necessary to control the solvents used during the coating process on the tablets. In herbal medicinal products, it is necessary to control the obvious decomposition products of herbal substances (herbal preparations) (for example, aglycones from anthraglycosides). For such degradation products, the acceptance criteria shall be established. If a significant amount of data is obtained from the relevant analytical methods that prove that herbal substances and (or) herbal preparations are not decomposed in this particular formulation and under specific storage conditions, tests for determining the content of degradation products can be reduced or eliminated (with the consent of the competent authorized body);

e) microbiological purity - it is necessary to indicate the total number of aerobic micro-organisms; total number of fungi; absence of specific bacteria. The number of micro-organisms shall be determined using pharmacopoeia or other validated methods. The acceptance criteria shall comply with the Pharmacopoeia of the Union and, in the absence of it, in the pharmacopoeias of Member States;

4. Specific tests and acceptance criteria

68. In addition to the universal tests given above, for specific herbal medicinal products, additional (specific) tests and acceptance criteria shall be included in the specification if they better characterize the quality of the medicinal product or are characteristic of the given dosage form.

Herbal medicinal products

69. Additional tests and acceptance criteria shall generally be included for specific herbal medicinal products. Below, as an example, a selection of

typical finished dosage forms of medicinal herbal products and their respective types of tests and acceptance criteria is presented. Finished dosage forms include solid oral herbal medicinal products and liquid oral herbal medicinal products. It is recommended to follow the principles of this document for other finished dosage forms.

Tablets (coated and uncoated) and hard capsules

70. Some of these tests can also be applied to soft capsules and granules.

a) dissolution (disintegration) - for herbal medicinal products with rapid release:

a test for the release of the active substance *in vitro* can be omitted if information on the components responsible for the therapeutic activity is not available;

it is sufficient to carry out only the disintegration test if the herbal medicinal product contains herbal preparations that are readily soluble throughout the physiological pH range;

usually it is sufficient to carry out the test at one point (one pH value).

Disintegration tests are most useful when the relationship between disintegration and dissolution is already established, or when the disintegration test is more significant than the dissolution test. In such cases, the dissolution testing is not always necessary, or it can only be carried out as part of a periodic inspection.

To justify the choice between the dissolution or disintegration testing, information shall be provided on the development of maintaining the stability of the formulation and the process.

For finished dosage forms with modified release, specific conditions for testing and sampling shall be established:

tests at several points (different pH values) for sustained release dosage forms;

two-stage tests at several points (using different media in series or in parallel) for sustained release dosage forms. In such cases, when developing tests and acceptance criteria, it is important to consider the population of patients who will take the herbal medicinal product (for example, patients with achlorhydria, elderly patients, etc.);

to establish acceptance criteria for several control points, the *in vitro - in vivo* correlation can be used (under condition that the biological availability data are available for humans or certain animal species for compositions showing different release rates). In the absence of such data and the impossibility to prove that the release of the medicinal product is not dependent on the in vitro testing conditions, the acceptance criteria shall be established based on the available data of the production series.

As a rule, the permissible fluctuation of the release rate at any time shall not exceed ± 10% of the declared content of a herbal substance or a herbal preparation (i.e. the allowable total fluctuation is 20%). Thus, the requirement (50 ± 10) % means that the allowable range is between 40% and 60% (except when the biological equivalent tests confirm a wider range);

b) strength (abrasion) - as a rule, it is sufficient to carry out tests for strength and (or) abrasion in the process control. In this case, there is usually no need to include these indicators in the specification. The acceptance criteria for these indicators are included in the specification if they are an important characteristic of the quality of the herbal medicinal product (e.g. chewable tablets);

c) homogeneity of dosage - pharmacopoeial methods shall be used. If appropriate, these tests can be carried out as a part of the control during the

production process, the acceptance criteria shall be included in the specification;

d) moisture content - a test for moisture content shall be included in the specification, where appropriate. The acceptance criteria can be justified by data on the effect of moisture or moisture absorption on a herbal medicinal product. In some cases, it is sufficient to carry out the test «Loss in mass during drying». However, it is necessary to provide a specific method for determining the moisture content (for example, Karl Fischer titration);

e) microbiological purity - a test for microbiological purity is one of the elements of the requirements of the Rules of Good Manufacturing Practice and quality control. It is allowed not to carry out tests for each series, if the original components are controlled, and the technological process is validated and does not create a risk of microbial contamination. It is expedient to conduct periodic tests. If necessary, the acceptance criteria shall be established for the total number of aerobic micro-organisms, the total number of fungi, the absence of specific micro-organisms (for example, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella spp.*, *Pseudomonas spp.*). Quantitative indicators shall be determined using pharmacopoeial or other validated methods, and the frequency and timing of sampling in the production process shall be justified by the accumulated data. In the presence of scientific justification, tests of microbiological purity for solid dosage forms can be avoided.

Liquids for oral use

71. Typically, for liquids for oral use and powders for preparing such liquid dosage forms, it is advisable to carry out one or more of the specific tests below.

a) homogeneity of dosing - this term includes both homogeneity of

content and homogeneity of the mass. Acceptance criteria shall be established for the deviations of mass, filling volume and (or) homogeneity of filling. In this case, pharmacopoeial methods shall be used. If necessary, tests can be carried out as a part of the control in the production process; but the acceptance criteria shall be included in the specification. This approach can be applied to packages for single or multiple reception. The dosage unit is considered as the standard dose taken by the patient. In the control test, this single dose can be determined by direct measurement or calculated from the measured total mass or volume of the medicinal product divided by the total expected number of doses. If a dispensing device is included in the package (for example, a medical pipette or a dispenser tip for vials), they shall be used to measure the dose. Otherwise, standard volume measuring devices shall be used. The device used for dosing is usually selected during the development process. For the powders intended for the preparation of liquids for oral use, it is considered acceptable to perform tests for the homogeneity of the mass;

b) pH value - if necessary, the acceptance criteria for pH shall be provided and the proposed range of values shall be justified;

c) microbiological purity - tests are not carried out for each series, if the original components are controlled, and the technological process is validated and does not create a risk of microbial contamination. It is expedient to conduct periodic tests. If there is a scientific justification, tests for the microbiological purity of the powders intended for dissolution and oral use may be omitted. Control is carried out in accordance with the Pharmacopoeia of the Union and, in the absence of it, in accordance with the pharmacopoeia of the Member States. If necessary, the acceptance criteria for the total number of aerobic micro-organisms, the total number of fungi, the absence of specific micro-organisms (for example, *Staphylococcus aureus*, *Escherichia coli*,

Salmonella spp., *Pseudomonas spp.*) shall be established. Quantitative indicators shall be determined using validated pharmacopoeial or other validated methods, and the frequency and timing of sampling in the production process shall be justified by the accumulated data.

d) the content of antimicrobial preservatives - for oral medicinal products containing antimicrobial preservatives, the acceptance criteria for their allowable content shall be established. The acceptance criteria shall be based on permissible limits that ensure compliance with microbiological quality of products over the shelf life. It is necessary to confirm the effectiveness of antimicrobial action with a minimum concentration of preservatives. As a rule, tests for the content of antimicrobial preservatives shall be carried out as a part of the control of the finished product. However, under certain circumstances, it may be sufficient to carry out tests within the control of the production process. If the control of the content of antimicrobial preservatives is carried out in the production process, the acceptance criteria shall be included in the specification for the finished product. The efficacy of an antimicrobial preservative shall be demonstrated during development, when scaled and over the shelf life (for example, as part of stability testing), even though the chemical analysis for preservative content is usually included in the specification;

e) the content of antioxidants - as a rule, the content of antioxidants shall be monitored as a part of the control of the finished product. In the presence of valid data obtained during the development process and study of the stability of finished medicinal products, tests over the shelf life may be omitted, and instead of testing within the control of finished products, it may be sufficient to conduct tests during the manufacturing process. If the control of the content of antioxidants is carried out in the production process, the acceptance criteria

shall be included in the specification for the finished product. With technological process, primary packaging is changed, the applied methods of control shall be re-evaluated;

e) extractable substances - tests are carried out if the primary package contains rubber (polymer) plugs, gaskets, covers, vials, etc. The components of the primary packaging shall be listed and information on these components shall be collected at the initial stage of the development process. If the data obtained at the stage of development of a medicinal product confirms that there is no extraction of substances from the primary packaging, there is no need to conduct such control. In case of change in the primary packaging, the method of controlling the extractable substances shall be re-analysed;

f) alcohol content - tests are carried out if the alcohol content is declared in the medicinal product;

h) dissolution - in addition to the quality indicators recommended above, in some cases (for example, when components of a herbal substance or a herbal preparation are difficult to dissolve), it is advisable to include a dissolution test and acceptance criteria for oral suspensions and dry re-suspension powders in the specification. If possible, equipment, dissolution medium and test conditions must meet the requirements of the Pharmacopoeia of the Union. Deviations from pharmacopoeial requirements shall be justified. Dissolution methods (both pharmacopoeial and non-pharmacopoeial) must be validated. As a rule, for finished dosage forms with rapid release it is sufficient to carry out tests at one point (one value). For finished dosage forms with controlled release, selective control at several fixed points (several values) shall be performed at appropriate intervals. The acceptance criteria shall be established based on the observed range of deviations, taking into account the dissolution profiles of the series that showed acceptable

characteristics in vivo. The dissolution test can be carried out both in the process control and in the output control, depending on its significance for product performance;

i) particle size distribution - particle size distribution tests and acceptance criteria for it are advisable to include in the specification for oral suspensions. If it is necessary to choose between the dissolution tests or the particle size distributions, the data obtained during the development process shall be used. The particle size distribution test can be carried out both in the process control and in the output control, depending on its significance for product performance. If during the development of a herbal medicinal product the rapid release of the medicinal product was confirmed, then the particle size distribution test in the specification may be not included. With the appropriate justification, the particle size distribution test may be carried out instead of the dissolution test. Acceptance criteria shall include the permissible particle size distribution (as a percentage of the total number of particles in a given range of sizes) and show the share (percentage) for intervals of different particle sizes. The average, upper and (or) lower limits of particle sizes shall be clearly defined. The acceptance criteria shall be established based on the observed range of deviations, taking into account the dissolution profiles of the series that showed acceptable characteristics in vivo and the intended use of the herbal medicinal product. During the development of a herbal medicinal product, the potential for increasing the particle size shall be investigated, and the results of these studies shall be taken into account when establishing the acceptance criteria;

j) redispersibility (recovery of dispersity) - the acceptance criteria for redispersibility is advisable for oral suspensions forming a residual during storage. A shaking test is acceptable. It is necessary to specify the method of

shaking (mechanic or Guideline) and clearly define the re-suspension time, based on the data obtained during the development of the herbal medicinal product. It is allowed conducting the sample tests of the series or to exclude this characteristic from the specification on the basis of information received at the development stage;

k) rheological properties (viscosity) - for relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity) in the specification. The test procedure shall be specified and the acceptance criteria shall be established. To justify the sample tests of the series or to exclude this indicator from the specification, data obtained during development may be sufficient;

l) specific gravity (density) - for oral suspensions, as well as viscous or non-aqueous solutions, it is advisable to include the specific gravity in the specification. Tests may be carried out as part of the control in the production process;

m) dissolution time - a test is provided for dry powders that are intended for reconstitution. The choice of a solvent shall be justified. To justify the sample tests of the series or to exclude this indicator from the specification, data obtained during development may be sufficient;

n) moisture content - in some cases for oral medicinal products that require dissolution, it is advisable to include a moisture content test in the specification and to set the acceptance criteria. The method for determining the moisture content is established based on the information obtained at the development stage. If the influence of the absorbed moisture on the medicinal product is reliably described during the development of the medicinal product, it is usually sufficient to carry out the «Loss in mass during drying» test. In certain cases (for example, in products containing essential oils), a specific

test is required (for example, Karl Fischer titration).

Herbal medicinal products containing exclusively herbal substances (herbal teas)

72. For the control of herbal medicinal products containing exclusively herbal substances, it seems appropriate to use one or more of the tests described below.

a) Loss in mass during drying - if this test has not been carried out as a part of the control of a herbal substance, it shall be added to the specification, depending on the part of the plants contained in the herbal medicinal product;

b) authenticity - authenticity tests (for example, using chromatographic methods) shall be specific for the herbal substance contained in the medicinal product, making it possible to detect differences between different components of herbal substances and surrogates / unwanted impurities that may be present. To confirm the authenticity, microscopic (macroscopic) characteristics can be used (if there is an appropriate justification);

c) purity - it is necessary to determine the related impurities and surrogates (for example, if toxic impurities and surrogates are known);

d) homogeneity of the mass (average weight of the package) (for example, of a herbal tea) - it is necessary to set the acceptance criteria for the deviations of mass and (or) the volume of filling. Pharmacopoeial methods shall be used. If it is justified, tests can be carried out as a part of the control during the production process; however, the acceptance criteria shall be included in the specification; This approach can be applied to dosage forms containing both a single dose and a multiple dose of the medicinal product. The dosage unit is taken as the standard dose taken by the patient. In the control test, this single dose can be determined by direct measurement or calculated from the measured total mass or volume of the herbal medicinal

product divided by the total expected number of doses. If the package contains a device for dosing, then it shall be used to measure the dose. Otherwise, a standard volume measure shall be used. The device used for dosing is usually selected during the development process;

e) quantitative determination - for medicinal products containing herbal substances having the components with known therapeutic activity, validated and detailed methods of quantitative determination of these components are necessary. If possible, the specification includes a specific method for controlling the stability of herbal substance in a herbal medicinal product. Non-specific definition (if justified) shall be combined with the specific test. For example, the quantitative determination of anthraquinon glycosides by a spectrophotometric method can be supplemented with the specific authenticity test (characteristic chromatogram - the «fingerprint» method). If the medicinal product contains herbal substances for which there is no information on the components responsible for their therapeutic activity, it is necessary to quantify active or analytical markers or conduct other validated tests. The choice of markers must be justified. For herbal medicinal products containing only herbal substances without any auxiliary substances, the quantification method can be included in the specification for the starting herbal substance. In cases of multicomponent herbal medicinal products, when it is not possible to quantify each name of herbal substance, it is necessary to justify how the reproducibility of the composition of the finished medicinal product is guaranteed and controlled;

f) particle size - the manufacturer must provide the proper specification;

g) microbiological purity - tests for microbiological purity are one of the elements of the quality assurance of the Rules of Good Manufacturing Practice and quality control. Tests may not be carried out for each series, if the

original components are controlled, and the technological process is validated and does not create a risk of microbial contamination. It is expedient to conduct periodic tests. If necessary, the acceptance criteria shall be established for the total number of aerobic micro-organisms, the total number of fungi, the absence of specific unwanted bacteria (for example, *Staphylococcus aureus*, *Escherichia coli, Salmonella spp.*, *Pseudomonas spp.*). Quantitative indicators shall be determined using validated pharmacopoeial or other validated methods, and the frequency and timing of sampling in the production process shall be justified by the accumulated data.