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THE EURASIAN ECONOMIC COMMISSION
BOARD

DECISION

September 07, 2018 **No. 151** Moscow

On approval of the Guidelines for preparation of the normative document on the medicinal product quality

In accordance with Article 30 of the Treaty on the Eurasian Economic Union dated May 29, 2014, as well as Articles 4 and 13 of the Agreement on Common Principles and Rules for Circulation of Medicinal Products within the Eurasian Economic Union dated December 23, 2014, the Board of the Eurasian Economic Commission **decided to:**

1. Approve the attached Guidelines for preparation of the normative document on the medicinal product quality.

2. This Decision shall come into effect 6 months after its official publication.

Chairman of the Board
of the Eurasian Economic Commission T. Sarkisian

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APPROVED

by Decision of the Board
of the Eurasian Economic Commission
No. 151 dated September 07, 2018

GUIDELINES
for preparation of the normative document on the medicinal product quality

I. General provisions

1. These Guidelines are developed taking into account Annex 3 to the Rules of authorisation and Assessment of Medicinal Products for Human Use, approved by the Decision of the Council of the Eurasian Economic Commission No. 78 dated November 3, 2016 (hereinafter – the Rules) and establishes the procedure for preparation of the normative document on the medicinal product quality (hereinafter – the normative document).

2. These Guidelines apply to the medicinal products regardless of their origin (chemical, biological, herbal, etc.).

3. The normative document establishes requirements for the medicinal products quality control (contains the specification and a description of test procedures or references to them, as well as the relevant acceptance criteria of quality indicators, etc.) on the basis of the medicinal product examination, and is approved by a authorised authority of the Member State of the Eurasian Economic Union (hereinafter, respectively, the Member State, the Union) during the medicinal product authorisation and is designed to control the post-authorisation medicinal product surveillance in the territories of the Member States.

4. The normative document is prepared exclusively in relation to the medicinal product. No normative document is required for an active pharmaceutical ingredient.

5. The normative document contains information on the quality of the medicinal product included in sections 3.2. P. 1, 3.2.P.5.1, 3.2.P.5.2, 3.2.P.7 and 3.2.P.8.1 of module 3 of the marketing authorisation application (Annex 4 to the Rules) and used by control laboratories of the Member States that do not have access to module 3 to perform the medicinal product quality control. The information contained in module 3 of the marketing authorisation application is of primary importance. The information contained in the normative document cannot contradict the information contained in module 3 of the marketing authorisation application dossier.

6. The normative document is prepared taking into account the instructions provided for in Annex 3 to the Rules.

7. Specifications for active pharmaceutical ingredients obtained by chemical synthesis and medicinal products containing such ingredients are prepared in accordance with Annex 1.

8. These Guidelines apply to the following dosage forms:

solid dosage forms for oral administration;

liquid dosage forms for oral administration;

parenteral dosage forms (large and small volumes).

The procedure of preparation of the normative document and specifications for these dosage forms may be applied to the other dosage forms.

9. General requirements for preparation of specifications for medicinal products and active pharmaceutical ingredients of biological origin are established in Chapter 6 of the Rules for conducting studies of biological medicinal products of the Eurasian Economic Union, approved by Decision of the Council of Eurasian Economic Commission dated November 3, 2016 No. 89.

10. General requirements for preparation of specifications for herbal medicinal products are established in the guidelines for selection of tests and

acceptance criteria for preparation of specifications for medicinal products derived from herbal substances approved by the Eurasian Economic Commission.

11. Requirements for preparation of specifications for certain types of medicinal products and active pharmaceutical ingredients included in their composition, depending on their dosage form or properties of the active ingredient, are determined by the relevant acts included in the law of the Union.

12. For the medicinal products specified in paragraphs 8 to 10 hereof, as well as radiopharmaceuticals, these Guidelines contain only requirements for the design of a normative document.

II. The structure of the normative document

13. The structure of the normative document must comply with Annex 3 to the Rules and contain 8 sections as follows:

a) title page in accordance with Annex 2;

b) medicinal product composition;

c) specification;

d) description of test procedures;

e) package description;

f) labeling;

g) storage conditions;

h) expiration date.

14. The quality indicators and regulated standards are given according to the manufacturer's specification at the end of the shelf life (expiration date). When there is the same quality indicator in the specifications for release and at the end of the shelf life (expiration date), the regulated standards for this indicator are given in the normative document according to the manufacturer's specification at the end of the shelf life (expiration date).

1. Title page

15. The title page of the normative document shall specify the following:

a) all brand names of a medicinal product approved by the authorised authority of the Member State and included in the marketing authorisation application dossier, as well as the dosage form in accordance with the Nomenclature of Dosage Forms, approved by the decision of the Board of the Eurasian Economic Commission No. 172 dated December 22, 2015;

b) dosage in accordance with the principles specified in the requirements for patient leaflets of medicinal products and summary of product characteristics for medical use, approved by the Decision of the Council of the Eurasian Economic Commission dated November 3, 2016 No. 88 (hereinafter - the requirements for the patient leaflet);

c) full and (or) abbreviated name and country of the marketing authorisation holder.

16. There should be special fields to specify the number of the normative document and stamp of approval. The requirements for specifying the number of the normative document are given in Annex 3 to the Rules. It is not allowed to list the participants of the medicinal products manufacture process in the normative document.

2. Medicinal product composition

17. The medicinal product composition is given in accordance with section 3.2.P.1 of module 3 of the marketing authorisation application (without specifying the functional purpose of excipients) in a separate section of the normative document by specifying the qualitative and quantitative composition of active pharmaceutical ingredients and excipients (with references to the Union Pharmacopoeia, and in the absence thereof - to the

pharmacopoeias of the Member States or to normative documents governing their quality).

18. The design of section 3.2. P. 1 of module 3 of the marketing authorisation application is given in Annex 1 to the Rules.

3. Specification

19. The specification must be a copy of the document contained in section 3.2.P.5.1 of module 3 of the marketing authorisation application dossier. The specification must be presented as a table consisting of 3 columns:

a) quality indicators;

b) standards (acceptable limits);

c) references to test procedures.

20. The quality indicators are established in accordance with the general pharmacopoeial monographs of the Union Pharmacopoeia, and in the absence thereof - in accordance with the general pharmacopoeial monographs of pharmacopoeias of the Member States, taking into account the characteristics of a particular dosage form of the medicinal product depending on the physico-chemical (biological) properties of the active pharmaceutical ingredient in accordance herewith.

21. The names of quality indicators in the specification are specified in accordance with the Union Pharmacopoeia, and in the absence thereof - in accordance with the pharmacopoeia of the reference Member State.

4. Description of test procedures

22. The description of the medicinal product testing procedures for all quality indicators listed in the specification, with references to the Union Pharmacopoeia, and in the absence thereof - to the pharmacopoeias of the Member States, is provided in accordance with section 3.2.P.5.2 of module 3

of the marketing authorisation application dossier.

5. Package description

23. Section 5 of the normative document must describe:

a) primary package (ampoules, vials, cans, bags, etc.);

b) the number of product units in the primary package (for example, the number of tablets per blister or strip packaging);

c) intermediate, secondary (consumer) packaging and the number of primary packages therein (for example, the number of blisters in the secondary packaging);

d) the presence of a moisture absorber, package leaflet (patient leaflet), completeness (needle, dropper, clip, etc.) and other information in accordance with section 3.2.P.1 of module 3 of the marketing authorisation application dossier. Further, the requirements for describing the nature and contents of the package are set out in section 6.5 of the requirements for the patient leaflet. The package description is not required, but if such information is mandatory, it should not contradict section 3.2.P.7 of module 3 of the marketing authorisation application dossier.

6. Labeling

24. Section 6 of the normative document must specify a reference to section 1.3.2 of module 1 of the marketing authorisation application dossier.

7. Storage conditions

25. Information about storage conditions must not contradict the information contained in section 3.2.P.8 of module 3 of the marketing authorisation application dossier.

26. General requirements for the description of storage conditions are

given in Annex 6 to the requirements for the patient leaflet.

8. Shelf life (expiration date)

27. The information included in section 8 of the normative document must not contradict the information contained in section 3.2.P.8 of module 3 of the marketing authorisation application dossier. General requirements for specifying the shelf life (expiration dates) are given in section 6.3 of the requirements for the patient leaflet.

III. Processing of a normative document

28. The text of the normative document must be brief, without repetitions, and exclude the eventual ambiguous interpretation. Abbreviations of words in the text, names of figures and diagrams are not allowed, except for the abbreviations contained in the specification and established by the Union Pharmacopoeia, and in the absence thereof - by the pharmacopoeias of the Member States.

29. The requirements for the medicinal product quality must be stated in the imperative form, and the test procedures in the third-person plural form.

30. If the test procedure, requirements for quality indicators, their normal ranges and deviations therefrom specified in the normative document are established by the Union Pharmacopoeia, and in the absence thereof - in the pharmacopoeias of the Member States, a reference to the source should be indicated without describing the test procedure. When specifying the requirements and quality indicators established by the pharmacopoeias of third-party states, a description of the test procedures used should be provided with a reference to the source.

31. The terms, designations, and definitions must correspond to the Union Pharmacopoeia, and in the absence thereof - to the pharmacopoeias of

the Member States. When using the terms and designations that are not established by acts of the Union bodies for medicinal products circulation (including the Union Pharmacopoeia) or pharmacopoeias of the Member States and are not generally recognized, their definitions should be given in the text.

32. The following shall not be allowed in the text:

a) use of colloquial phrases;

b) use of different terms that are similar in meaning (synonyms) to denote the same concept, as well as foreign words and terms if there are equivalent words and terms in the Russian language;

c) abbreviations of the units of measurement, if they are used without numbers;

d) replacement of words with letter symbols (except for tables and formulas);

e) use of mathematical signs without numbers.

33. When describing analytical procedures for the reagents used, standard solutions, buffer solutions and materials, it is necessary to specify the designations of standards or specifications, as well as the full and (or) abbreviated name of the manufacturing company. If the Union Pharmacopoeia or the pharmacopoeias of the Member States contain descriptions of reagents, reference solutions, buffer solutions, and materials used in tests, their names must be italicized, followed by "P" designation. If the Union Pharmacopoeia or the pharmacopoeias of the Member States does not contain a description of the reagents used, reference standards, buffer solutions, and materials, it is necessary to indicate the designations of the standards or specifications governing the same, as well as the name of the manufacturing company. The names of titrated solutions described in the Union Pharmacopoeia or in the pharmacopoeias of the Member States are also italicized, without the "P" designation. For the graduated ware used, its capacity must be indicated.

34. Calculation formulas should be presented in expanded and abbreviated forms and accompanied by an explanation of the physical quantities specified therein. Designations of physical quantities must be given in accordance with the Union Pharmacopoeia, and in the absence thereof - in accordance with the pharmacopoeias of the Member States. It is not allowed to transfer a part of the calculation formula to another line.

35. For the measurement of physical quantities specified in the normative document, the units of the International System of Units (SI) and the units of measurement used along with them must be utilized.

36. The text of the normative document is made taking into account the following settings:

field sizes: left - 30 mm, right - 15 mm, top and bottom - 20 mm;

paragraph indent - 12.5 mm;

times New Roman font size 14 (for the number of the normative document - 16).

Titles and the name of the medicinal products shall begin with an uppercase letter and are highlighted in bold.

The main text is printed in 1.5 line spacing, the text in the specification and notes - in 1 line spacing, and the text in the titles and in the description of the qualitative and quantitative composition - in 1 line spacing (if different names are specified - in 1.5 line spacing).

37. The pages of the normative document should be numbered. However, the number must not placed on the first page.

38. Figures, charts, diagrams, graphs, spectra, and chromatograms can be made on separate pages or in the text of a normative document.

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ANNEX 1

to the Guidelines
for preparation of the normative
document on the medicinal product
quality

REQUIREMENTS
for the preparation of specifications: analytical procedures and acceptance criteria for active substances obtained by chemical synthesis, and medicinal products containing the same

I. General characteristics

1. These Requirements contain a description of approaches to the development of a single set of specifications for active pharmaceutical ingredients (active ingredients) and (or) medicinal products, including the recommendations for the development and justification of acceptance criteria (acceptable standards) and the choice of analytical procedures for active pharmaceutical ingredients obtained by chemical synthesis and medicinal products containing the same.

2. The specification must list a set of criteria that active pharmaceutical ingredients and/or medicinal products must meet in order to be considered suitable for their intended use. Compliance with the specification means that the active pharmaceutical ingredients and/or medicinal products meet the specified acceptance criteria, provided that the tests are performed according to the analytical procedures specified in it. Specifications are the key quality standards that are proposed and justified by the manufacturer and approved by the authorised authority of the Member State of the Eurasian Economic Union (hereinafter, respectively, the Member States, the Union) during the medicinal product authorisation.

Specifications are a part of the overall control strategy for active pharmaceutical ingredients and/or medicinal products designed to ensure their

quality and consistency of characteristics. The other elements of this strategy include thorough prescription of all the characteristics of the active pharmaceutical ingredients, intermediate products and (or) medicinal products (hereinafter - the products) in the course of the medicinal product development, as well as strict observance of the Good Manufacturing Practice of the Eurasian Economic Union, approved by Decision of the Council of the Eurasian Economic Commission dated November 3, 2016 No. 77 (hereinafter - the GMP), for example, suitable premises and equipment, validated manufacturing process of a medicinal product, validated analytical procedures, testing of starting and raw materials, in-process testing, stability testing, etc.

Specifications are intended to confirm the quality of an active pharmaceutical ingredient and a medicinal product. They are not intended to establish the comprehensive characteristics and should therefore be based on the characteristics that have proven their ability to ensure the safety and efficacy of an active pharmaceutical ingredient and a medicinal product.

II. Scope

3. The quality of active pharmaceutical ingredients and/or medicinal products shall be determined by the level of development, in-process control, compliance with the Good Manufacturing Practice, validation of the production process, as well as the specifications applied thereto during the development and manufacture. These Requirements define the requirements for the specification, i.e., those tests, procedures, and acceptance criteria that ensure the quality of an active pharmaceutical ingredient and a medicinal product at the time of release and during the entire shelf life. Specifications are an important, but not the only component of quality assurance for active pharmaceutical ingredients and medicinal products.

4. These Requirements apply to the medicinal products (including the

active pharmaceutical ingredients forming a part thereof) pending the authorisation. These Requirements do not cover active pharmaceutical ingredients and/or medicinal products pending the clinical development.

These Requirements may apply to synthetic and semi-synthetic antibiotics, as well as low molecular weight synthetic peptides, but they are not sufficient to describe the specifications of high molecular weight peptides and polypeptides, as well as biotechnological (biological) preparations properly.

Radiopharmaceuticals, fermentation products, oligonucleotides, herbal preparations, and untreated preparations of animal and herbal origin are out of the scope of these Requirements.

5. These Requirements provide recommendations for acceptance criteria to be developed for all active pharmaceutical substances and/or medicinal products, i.e. general acceptance criteria, as well as special acceptance criteria provided for individual active pharmaceutical ingredients and/or medicinal products. These Requirements should be considered as the main guide for the preparation of specifications and selection of acceptance criteria. However, when new analytical technologies and modifications to the existing technologies are introduced, their data should also be used subject to a sufficient justification.

6. These Requirements address the following dosage forms:

a) solid dosage forms for oral administration;

b) liquid dosage forms for oral administration;

c) parenteral dosage forms (in large and small volumes).

7. The dosage forms specified in paragraph 6 hereof serve as models that may be applicable to the other dosage forms. When preparing specifications for the other dosage forms (for example, inhalation (powders, solutions, etc.), topical dosage forms (creams, ointments, gels) and transdermal dosage forms), it is advisable to expand the concepts used herein.

8. These Requirements provide a brief description of each concept and indicate the circumstances in which they may be applied. As a rule, proposals for the application of these concepts must be justified by the applicant and approved by the authorised authority of the Member State before release.

III. Definitions

9. For the purposes of these Requirements, the concepts shall be used having the following meanings:

"rapidly dissolving medicinal products"; a solid medicinal product for oral administration with immediate release shall be considered rapidly dissolving if at least 80 % of the declared content of the active substance is dissolved within 15 minutes in each of the following media: at pH 1.2, 4.0, and 6.8;

"in-process tests" are the tests performed during the manufacturing process of an active substance and (or) a medicinal product, and not as a part of a set of tests conducted before release into circulation;

"combined medicinal product" means a medicinal product containing more than one active substance;

"immediate release" means the process of medicinal product dissolution in the gastrointestinal contents without the intention of delaying or prolonging its dissolution or absorption;

"delayed release" means the release of an active substance at the time that does not coincide with the time of release after immediate ingestion;

"polymorphism" means different crystalline forms of the same active substance, including in the form of solvatation or hydration products (pseudopolymorphs) and amorphous forms;

"a degradation product" means a molecule formed as a result of chemical changes in the molecule of the active substance over time and/or under the

influence of light, temperature, pH, moisture, etc. or when interacting with an excipient and/or a packaging (closure) system;

"prolonged release" means the process of the active substance release for a long period after administration;

"solvent" means an inorganic or organic liquid used as a medium for the preparation of solutions and suspensions in the course of the active substance synthesis or medicinal product manufacturing;

"racemate" means a mixture (solid, liquid, or gaseous) or a solution of equimolar amounts of two enantiomers. Does not feature optical activity;

"specific test" means a test that is considered applicable to certain active substances and/or certain medicinal products, depending on their characteristics and/or intended use;

"reference standard (reference material)" means a substance used as a reference for quantitation, identification, or purity testing;

"generic test" means a test that is considered potentially applicable to all active substances and/or all medicinal products (for example, tests for description, identification, quantitation, and determination of impurities);

"active substances highly soluble in water" means active substances with a ratio of "substance dose/solubility" less than or equal to 250 ml in the pH range of 1.2 to 6.8 (for example, compound A has the lowest solubility of 1 mg/ml at 37 ± 0.5 °C and pH 6.8 and is presented in three strengths, 100, 200, and 400 mg. Such a medicinal product shall be considered slightly soluble, since its ratio "substance dose/solubility" is 400 ml (400 mg : 1 mg/ml = 400 ml) and thus exceeds 250 ml);

"chiral" means not coinciding when a specular reflection is imposed; it is applicable to molecules, conformations, and macroscopic objects (e.g., crystals). This term shall also apply to the samples of substances with chiral molecules, even if the macroscopic set of molecules is a racemate;

"enantiomers" mean isomers having the same composition and chemical structure, but different spatial arrangement of the atoms in the molecule and incompatible mirror images.

For the purposes hereof, the term of "impurity" shall have the meaning defined in the Good Manufacturing Practice, the term of "acceptance criteria" shall have the meaning defined in the Guidelines on quality of herbal medicinal products (Annex to the Recommendation of the Board of the Eurasian Economic Commission dated May 10, 2018 No. 6), the term of

"modified release" shall have the meaning defined in the Guidelines on quality of oral modified-release products (Annex to the Recommendation of the Board of the Eurasian Economic Commission dated February 16, 2018 No. 2).

IV. Types of tests

1. Periodic (random) testing

10. Periodic (random) testing means performing certain tests at release on pre-selected batches of an active pharmaceutical ingredient and (or) medicinal products (hereinafter referred to as the batches) and (or) at pre - determined intervals (and not for each batch). At the same time, the batches that are not subject to testing must also meet all the acceptance criteria provided for the active pharmaceutical ingredient and/or medicinal products. The performance of such a test is an incomplete testing program, and, therefore, it must be justified and submitted for approval to the authorised authority of the Member State before the start of the test. This approach is applicable, for example, to the tests for residual solvents and microbiological purity intended for solid dosage forms for oral administration. When submitting the marketing authorisation application dossier, the applicant can only have limited data, so this approach should be implemented at the post-

authorisation stage. If any non-compliance with the approved acceptance criteria is found during periodic (random) tests, the authorised authorities of the Member States must be duly notified. If these inconsistencies indicate that routine testing needs to be resumed, one should re-launch the tests at release for each batch.

2. Acceptance criteria at release and during shelf life

11. The approach associated with the difference in the acceptance criteria for specifications at release and during shelf life shall apply only to medicinal products. It provides for the establishment of stricter acceptance criteria for the medicinal product release in comparison with the acceptance criteria applied during the shelf life. For the application of this approach, the examples of indicators include quantitation and the related impurities.

12. The applicant may establish more strict limits of acceptance criteria at release to provide confidence that the quality of the medicinal product will remain within the regulatory acceptance criterion throughout the shelf life.

3. In-process testing

13. In-process tests mean the tests that may be performed during the manufacturing process of an active pharmaceutical ingredient and (or) a medicinal product, and not as a part of an official set of tests conducted before the product release.

14. The specification does not include in-process tests that are used to correct the process parameters within the operating range set for this process (for example, the hardness and brittleness of the tablet cores to be coated, and the weight of individual tablets).

15. Certain tests performed during the manufacturing may be sufficient to confirm compliance with the specification if the same tests are included in

the specification, and the acceptance criterion is identical to the requirement set out in the specification used for release, or is stricter (for example, the solution pH).

16. However, this approach needs to be validated to prove that the functional characteristics of the intended product or the results of its in-process tests have not changed in relation to the finished product.

4. Design and development issues

17. Specifications should be based on the experience and data accumulated during the development of an active pharmaceutical ingredient and/or medicinal product. Based on this data, one can make suggestions to exclude, add, or replace certain tests. For example, one may exclude:

a) microbiological purity tests for active pharmaceutical ingredients and (or) solid dosage forms, which have confirmed the inability to maintain the viability and growth of microorganisms during the development process (decision diagrams 6 and 8);

b) identification of substances extracted from the package if it has been proved with reproducible results that the extracted substances are not detected in the medicinal product or their content meets acceptance criteria and safety requirements;

c) a particle size determination test, depending on the significance for the product functional characteristics (it can be performed as a test during manufacturing process or at release).

18. The dissolution test of solid dosage forms for oral administration with immediate release containing active pharmaceutical ingredients that are rapidly soluble in water may be replaced by a test for disintegration test, if such medicinal products show a constant rapid release of the active substance during the development (decision diagrams No. 7(1) and 7(2)).

5. Problems of restricted quality of the data when submitting the marketing authorisation application dossier

19. At the time of filing the marketing authorisation application dossier, the data on its quality may be limited, which may affect the process of establishing the acceptance criteria. In this regard, as the experience of manufacturing a particular active pharmaceutical ingredient and/or medicinal product is gained, it may be required to review the acceptance criteria (for example, the acceptance criteria for the content of a specific impurity). The acceptance criteria at the time of the marketing authorisation application submission shall be established on the basis of safety and efficacy requirements.

20. If there is only limited data on the quality of the medicinal product at the time of approval of the tests and acceptance criteria, previously approved tests and acceptance criteria shall be reviewed as information accumulates, taking into account the eventual modifications of tests and acceptance criteria. Both less and more strict acceptance criteria can be established.

6. Release by parameters

21. Release by parameters as an alternative to routine tests at release can be used in limited cases and only if approved by the authorised authority (for example, replacement of the sterility test for medicinal products undergoing final (terminal) sterilization, subject to their release by parameters). If the sterility test is replaced with release by parameters, the release of each batch is based on satisfactory results of certain parameter monitoring (temperature, pressure, and duration of the terminal sterilization phases during medicinal product manufacturing). These parameters can usually be monitored and measured with greater accuracy, so they are a more reliable sterility indicator

than the final product sterility test. Appropriate laboratory tests (for example, the use of a chemical or physical indicator) can be included in the program of release by parameters. Before introducing the release by parameters, the sterilization process must be validated properly. It is also required to confirm the preservation of the validated condition by performing revalidation at set intervals. During release by parameters, the specification must include a quality indicator (for example, sterility) that is controlled indirectly, as well as a reference to the associated analytical procedure.

7. Alternative test procedures

22. Alternative test procedures are the procedures that may be used to determine the quality indicator, if they allow controlling the quality of an active pharmaceutical ingredient and/or a medicinal product to the same extent as an officially approved procedure, or to a higher degree. For example, for tablets that have been proven not to decompose during the manufacturing process, it is allowed to use a spectrophotometric procedure, rather than an officially approved chromatographic procedure, for the purpose of release quality control. However, in order to confirm compliance with the acceptance criteria during the medicinal product shelf life, it is required to use a chromatographic procedure.

8. Pharmacopoeia tests and acceptance criteria

23. In the Union Pharmacopoeia, and in the absence thereof in the pharmacopoeias of the Member States, certain procedures (hereinafter referred to as pharmacopoeia procedures) or references thereto are given. Pharmacopoeial procedures must be used in all cases (as appropriate).

9. Emerging technologies

24. As new analytical technologies are continuously being developed and the existing ones are being amended, the developing technologies should be used if they provide additional quality assurance or if their use is justified for the other reasons in terms of ensuring the medicinal product quality or safety.

10. Influence of an active pharmaceutical ingredient on the medicinal product specification

25. As a rule, it is not required to conduct the medicinal product tests by quality indicators that are specific only to active pharmaceutical ingredients. For example, a medicinal product does not need to be tested for the presence of impurities that are controlled in an active pharmaceutical ingredient and are associated with the synthesis process, rather than being degradation products. Learn more in the rules for the study of impurities in medicinal products and the establishment of requirements for the same in the specifications approved by the Eurasian Economic Commission (hereinafter - the Commission).

11. Reference standard

26. The quality of the reference standard must correspond to its purpose. A reference standard is often characterized and evaluated for suitability for its intended purpose using additional procedures and methods. In reference standards of an active pharmaceutical ingredient intended for use in quantitation tests, it is required to identify properly and/or control the impurities and determine the purity using a quantitative procedure.

V. Requirements for specifications

1. Specifications: definition and justification

Definition of specifications

27. In addition to the tests at release, the specification may contain a list

of tests performed during the manufacturing process, periodic (random) tests and other tests that are not always performed for each batch. In such situations, the applicant must indicate which tests are performed for each batch and which are not. In this case, one must specify and justify the selection and frequency of tests. An active pharmaceutical ingredient and/or medicinal product must meet the acceptance criteria if they are being tested. It should be noted that amendments to the specifications after approval of the medicinal product marketing authorisation application may request the preliminary examination by the authorised authority of the Member State.

Justification of specification

28. During the initial preparation of the specification, it is required to justify each proposed analytical procedure and each acceptance criterion. The justification should refer to the relevant development data, the requirements of the Union Pharmacopoeia, and in the absence of relevant data therein – to the requirements of the pharmacopoeias of the Member States, the results of testing the active pharmaceutical ingredients and (or) medicinal products used in toxicological and clinical studies, as well as the results of accelerated and long-term stability tests. Further, it is required to take into account acceptable ranges of probable variability of the analytical procedure and probable variability of the medicinal product manufacturing process.

29. Additional approaches not described herein may be applicable and reasonable. The use of such alternative approaches requires justification by the applicant. When justifying the specifications, it is required to follow the data obtained from the results of the synthesis of an active pharmaceutical ingredient and (or) the medicinal product manufacturing process. In this case, theoretically acceptable limits for a specific procedure or a specific acceptance criterion can be considered as a justification. However, regardless of the

approach used, the experimental actual results shall be fundamental.

30. When preparing and justifying specifications, the test results of the batches included in the stability test program, as well as batches obtained during scaling (validation) of the process should be taken into account, and special attention should be paid to the initial batches used for stability tests. If one plans to use several production sites, it is advisable to take into account the data obtained at these sites during initial selection of the main tests and acceptance criteria. It i required when there is insufficient initial experience in the production of an active pharmaceutical ingredient and/or a medicinal product at this production site. When one representative production site is used to select the tests and acceptance criteria, the product manufactured at the other sites must meet these criteria.

31. When justifying individual acceptance criteria, it is recommended to present the test results in graphical form (in particular, the values of the quantitative content of an active pharmaceutical ingredient and related impurities). When the results are presented in this form, the specification must include the data obtained at the development stage, as well as available data on the stability of a batch of an active pharmaceutical ingredient or a medicinal product manufactured using the proposed medicinal product manufacturing process.

32. When justifying an exclusion of a test from the specification, one must follow the data on the development and validation of the medicinal product manufacturing process (if applicable).

2. Generic tests (criteria)

33. When fulfilling the requirements specified in paragraphs 34 to 36 hereof, it is also required to take into account the Guidelines for validation of the analytical procedures for medicinal products testing, approved by the

Decision of the Board of the Eurasian Economic Commission dated July 17, 2018 No. 113.

Active substances

34. The following tests and acceptance criteria apply to all active pharmaceutical ingredients:

a) appearance means a qualitative characteristic of the physical state (for example, solid, liquid) and color of an active pharmaceutical ingredient. If one of these properties changes during storage, one must investigate the same and take the required steps;

b) identification; identification tests should allow the best distinguishing between compounds with a closely related structure that may be present in an active pharmaceutical ingredient and/or medicinal product with a high probability. Identification tests should be specific to an active pharmaceutical ingredient (for example, by infrared spectroscopy). Identification by chromatographic retention time alone is not considered specific. However, the use of two chromatographic techniques, where the separation of detectable substances is based on different principles, or a combination of tests into a single procedure (for example, HPLC/UV on a diode matrix, HPLC/MS or GC/MS) is acceptable. If an active pharmaceutical ingredient is a salt, the identification test must be specific to each of the ions. A test specific to the salt may be sufficient. For optically active pharmaceutical ingredients, it may be required to conduct a specific test to identify them or to perform a quantitation specific to the chiral compound;

c) quantitation - to determine the content of the active pharmaceutical ingredient in the analyzed sample, it is required to include a specific procedure allowing to obtain stable results into the specification. In many cases, it is allowed to use the same procedure (for example, HPLC) both for the

quantitation of an active pharmaceutical ingredient and for the determination of the impurity content. If a justification for using a non-specific quantitation procedure is provided, the other supporting test procedures must be used to achieve overall specificity. For example, if titration is used to quantify an active pharmaceutical ingredient, a combination of quantitation and a suitable impurity test must be used;

d) impurities - the specifications must specify organic and inorganic impurities, as well as residual solvents. Extrapolation of significant limits of the impurity content based on the data obtained during development is described in the decision diagram No. 1. Since there may be insufficient data to assess the process consistency at the time of the marketing authorisation application submission, it is not appropriate to establish the acceptance criteria that only cover batch analysis data available at the time of the marketing authorisation application submission.

Medicinal products

35. The following tests and acceptance criteria shall apply to all medicinal products:

a) appearance - the specification shall describe the quality characteristics of the dosage form (for example, size, shape, and color). If one of these properties changes during the medicinal product manufacturing process or during its storage, such a change must be investigated and the required steps must be taken. Acceptance criteria should include the medicinal product appearance. If the medicinal product appearance changes color during storage, then the specification requires the inclusion of a quantitation procedure;

b) identification - tests should establish the identity of an active pharmaceutical ingredient in the medicinal product, as well as allow distinguishing between the compounds with a closely related structure that

may be present in the composition of an active pharmaceutical ingredient and (or) medicinal product with a high probability. Identification tests should be specific to an active pharmaceutical ingredient (for example, by infrared spectroscopy). Identification by chromatographic retention time alone is not considered specific. It is generally acceptable to use two chromatographic procedures where separation is based on different principles, or to combine tests into a single procedure (for example, HPLC/UV on a diode matrix, HPLC/MS, or GC/MS);

c) quantitation - the specification must include a specific quantitation procedure that allows obtaining stable results for all medicinal products to determine the content. In many cases, it is allowed to use the same procedure (for example, HPLC) both for the quantitation of an active pharmaceutical ingredient and for the determination of the impurity content. For the quantitation of an active pharmaceutical ingredient in medicinal products, the results of tests for the content uniformity may be used, if they are also acceptable for quantitation. If the rationale for using a non-specific quantitation procedure is presented, the other supporting analytical procedures must be used to achieve overall specificity. For example, if titration is used to quantify an active pharmaceutical ingredient, a combination of quantitation and a suitable impurity test must be used. Where the data on the effect of excipients on the test results are available when using a non-specific quantitation procedure, a specific procedure must be used;

d) impurities - the specification must list organic and inorganic impurities, degradation products, and residual solvents. Organic impurities formed during the degradation of an active pharmaceutical ingredient and impurities formed during the medicinal product manufacturing are subject to control. Acceptable limits should be set for the content of individual specified degradation products, which may be either identified or unidentified

degradation products, as well as the limits for the total content of degradation products. Impurities formed during the synthesis of an active pharmaceutical ingredient are usually controlled at the testing stage and are not included in the limit of the sum of impurities. If the process impurity is also a degradation product, its content must be controlled and included in the limit of the sum of degradation products. If it is clearly proved using an appropriate analytical procedure that the active pharmaceutical ingredient that is a part of a specific medicinal product is not degraded under specific storage conditions specified in the marketing authorisation application dossier, then after the said medicinal product authorisation, in agreement with the authorised body, it is allowed to reduce the volume of testing for degradation products or exclude it from the specification.

36. Decision diagram No. 2 shall describe the extrapolation of significant limits on the content of degradation products based on the data obtained during development. At the time of the marketing authorisation application submission, there is usually insufficient data to assess the consistency of the medicinal product manufacturing process. In this regard, it is not appropriate to establish the acceptance criteria that cover only the batch analysis data available at the time of the marketing authorisation application submission.

3. Specific tests (criteria)

37. In addition to the generic tests specified in paragraphs 34 to 36 hereof, the following additional tests are required for certain active pharmaceutical ingredients and/or medicinal products. If the test affects the quality control of a batch of active pharmaceutical ingredients and/or medicinal products, individual tests (criteria) must be included in the specification. In some cases (for example, after the accumulation of data on changes in the medicinal product quality), the other tests may be required.

Specific tests (criteria) for active substances

38. The following specific tests (criteria) are applicable to all active substances:

a) physical and chemical properties. These include, but not limited to, the pH of the aqueous solution, the melting point (temperature range), and the refractive index. The procedures used to determine these properties are usually unique and do not require complex measurements (for example, the capillary method for determining the melting point, Abbe refractometry). Tests performed to confirm the physical and chemical properties must be determined based on the physical and chemical properties of an active pharmaceutical ingredient and its intended purpose;

b) particle size. For some active pharmaceutical substances intended for use in solid medicinal products or suspensions, particle size can have a significant effect on the dissolution rate, bioavailability, and/or stability. In such cases, the acceptance criteria should be established and a particle size test should be performed using an appropriate procedure. Decision diagram No. 3 provides additional clarification in respect of the existing cases of particle size determination tests;

c) polymorphic forms. Some active pharmaceutical substances exist in different crystalline forms with varying physical properties. Polymorphism can also include the products of solvatation and hydration (pseudopolymorphs), as well as amorphous forms. Differences in the profile of these forms may in some cases affect the quality and functional characteristics of medicinal products. When there are differences with the proven effect on the medicinal product functional characteristics, bioavailability or stability, the specification must indicate the corresponding state of the solid substance. Physical and chemical measurements and methods are usually used to determine the presence of

several polymorphic forms (for example, the melting point (including the high temperature microscopy), infrared spectroscopy (IR) for solid substances, powder x-ray diffraction, and thermal analysis procedures (including the differential scanning calorimetry (DSC),

thermogravimetric analysis (TGA) and differential thermal analysis (DTA)), Raman spectroscopy, light microscopy, and nuclear magnetic resonance (NMR) spectroscopy for substances in the solid state). Decision diagrams No. 4 (1) to 4 (3) provide additional explanations of when and how to control and check polymorphic forms. These decision diagrams should be applied consistently. Decision diagrams No. 4 (1) and 4 (2) consider whether an active pharmaceutical ingredient exhibits polymorphism and whether different polymorphic forms can affect the functional characteristics of the medicinal product. Decision diagram No. 4 (3) should be used if an active pharmaceutical ingredient shows polymorphism and it affects the functional characteristics of the medicinal product. Using the decision diagram No. 4 (3), it is possible to analyze the possibility of changing the profile of polymorphic forms in a medicinal product, as well as the ability of such a change to affect its functional characteristics.

As a rule, it is technically very difficult to measure the polymorphic changes in medicinal products. In order to control the medicinal product functional characteristics, indirect tests (for example, dissolution) are usually used (decision diagram No. 4 (3)), and the determination of the polymorphic form content, as well as the establishment of acceptance criteria for such a test should only be performed as the last resort;

d) tests for chiral active pharmaceutical ingredients. If the active pharmaceutical ingredient is predominantly one enantiomer, and the content of the opposite enantiomer is below the qualification and identification thresholds given in the rules for the study of impurities in medicinal products and the

establishment of requirements for the same in specifications approved by the Commission, the opposite enantiomer shall not be determined due to the practical complexity of determining its low content. However, such impurity in the chiral active pharmaceutical ingredient and its corresponding medicinal product should be controlled in accordance with the rules for the study of impurities in medicinal products and the establishment of requirements for the same in specifications. Decision diagram No. 5 summarizes the terms and conditions that require testing for identification of chiral compounds, tests for determination of impurity content, as well as quantitation for both active pharmaceutical ingredients and medicinal products in accordance with the following concepts.

Active pharmaceutical ingredients: impurities. The control of the opposite enantiomer of chiral active pharmaceutical ingredients developed as a single enantiomer shall be performed in the same way as for the other impurities. However, technical restrictions may prevent the use of the same quantitation or qualification limits. Using the appropriate justification, the reliability of control should also be demonstrated by suitable tests of the feedstock or intermediate product.

Quantitation. The specification shall include a quantitative test for the active pharmaceutical ingredient, which allows the selective determination of the enantiomer content in the active pharmaceutical ingredient.

To meet these terms and conditions, it is considered acceptable to use a chiral compound-specific quantitation procedure with appropriate enantiomeric impurity control methods.

Identification. For an active pharmaceutical ingredient developed as a single enantiomer, identification tests should be able to distinguish between each enantiomer and a racemic mixture of enantiomers. There are two cases in which an active pharmaceutical ingredient, which is a racemic mixture,

requires a test for the identification of stereoisomers during tests at release (suitability tests) when there is a high probability of the racemate replacement with an enantiomer or grounds for selective crystallization, which may lead to the unintended formation of a non-racemic mixture.

Medicinal product: degradation products. In the absence of a proof that racemization is insignificant during the production of the dosage form and its storage, it is required to monitor the content of the second enantiomer in the medicinal product.

Quantitation. If it is proved that racemization is insignificant during the production and storage of the dosage form, it is allowed to use a quantitation procedure that is non-specific for the chiral compound. In other cases, it is required to use a procedure specific to the chiral compound, or alternatively a combination of a non-specific procedure and a validated method to monitor the content of the opposite enantiomer.

Identification. A stereospecific identification test is usually not included in the medicinal product specification at the time of release. If racemization is negligible during the production and storage of the dosage form, it is advisable to include a stereospecific identification test in the specification of an active pharmaceutical ingredient. If racemization occurs in the dosage form, a chiral quantitation procedure or a test for enantiomeric impurity in the medicinal product is used to confirm the identity;

e) water content. This test is performed if an active pharmaceutical ingredient is hygroscopic, or moisture causes its degradation, or an active pharmaceutical ingredient is a stoichiometric hydrate. Acceptance criteria can be justified using the data on the effects of hydration or moisture absorption. In some cases, it is sufficient to use a procedure for determining the mass loss during drying, but it is preferable to use a detection procedure specific to water (for example, Fischer titration);

f) inorganic impurities. Based on the data obtained during development, and based on knowledge of the medicinal product manufacturing process, the need to include tests and acceptance criteria for inorganic impurities (for example, catalysts) should be determined. The procedures and acceptance criteria for sulphate ash (total ash) must meet the requirements of the Union Pharmacopoeia, and in the absence of relevant data, the requirements of the pharmacopoeias of the Member States. The other inorganic impurities can be determined using the other suitable procedures (for example, atomic absorption spectrometry);

g) microbial limits. The specification may require specifying the total content of aerobic microorganisms, the total number of yeast and mold fungi, as well as information about the complete absence of certain types of bacteria that are not allowed in the medicinal product (for example, *Staphylococcus aureus, Escherichia coli, Salmonella spp., Pseudomonas aeruginosa).* The presence of microorganisms must be determined using pharmacopoeial procedures. The type of microbial tests and acceptance criteria should be determined based on the properties of an active pharmaceutical ingredient, the manufacturing method and the proposed use of the medicinal product. For example, for sterile active pharmaceutical ingredients, it is advisable to conduct a sterility test, and the endotoxin test should be performed with an active pharmaceutical ingredient used to manufacture the injectable medicinal products. Decision diagram No. 6 provides the further explanation of the cases when microbial limit tests shall be included in the specification.

Specific tests (criteria) for the medicinal products

39. The list specified in paragraphs 40 and 41 hereof is a representative list of the medicinal products, as well as the types of tests and acceptance criteria that should be included in their specifications. The list includes solid

and liquid dosage forms for oral administration and parenteral dosage forms (small and large volumes). The principles specified in paragraphs 40 and 41 hereof may be applicable to the other dosage forms.

Tablets, film-coated tablets, and capsules

40. The following tests may be applicable to soft capsules and granules:

a) dissolution. The specification of solid dosage forms for oral administration usually includes tests to determine the release of an active pharmaceutical ingredient from the medicinal product. For immediate-release dosage forms, "single-point" measurements are usually sufficient. For modified-release dosage forms, appropriate test conditions and sampling procedures must be selected. For example, for long-release dosage forms, sampling should be performed at several time points, and for delayed-release dosage forms, it is advisable to conduct a two-stage test (sequentially or in parallel, using different media, depending on the situation). In such cases, the selection of trials and the establishment of acceptance criteria should take into account the population of people to whom the medicinal product is intended (for example, elderly people suffering from achlorhydria). In some cases, the dissolution test may be replaced by a disintegration test (decision diagram No. 7 (1)).

If a change in the rate of dissolution of immediate-release medicinal products can significantly affect bioavailability, it is recommended to provide for the testing conditions, which can detect batches with unacceptable bioavailability. If changes in the composition or parameters of the medicinal product manufacturing process significantly affect the dissolution and such changes are not controlled by another method provided for in the specification, it is advisable to provide for the dissolution test conditions that will allow recognizing such changes (decision diagram No. 7 (2)).

If the dissolution significantly affects the bioavailability, then it is required to establish the acceptance criteria for the dissolution test, allowing the rejection of batches with unacceptable bioavailability. In other cases, it is required to select such test conditions and acceptance criteria that will allow the selection of medicinal product batches suitable for the medicinal product use for medical purposes (decision diagram No. 7 (2)).

For medicinal products with prolonged release of different compositions showing different release rates, in order to establish the acceptance criteria, it is allowed to use in vivo (in vitro) correlation to justify them, if there is data on the bioavailability of such medicinal products in humans. If human bioavailability data are not available and it is not possible to confirm that the release of an active pharmaceutical ingredient is independent of in vitro test conditions, then the acceptance criteria shall be established based on the available batch test results. The permissible deviations of the average release rate at all time points should not exceed ± 10 % of the declared active pharmaceutical ingredient content (i.e., the total variability is not more than 20 %: the requirement of 50 ± 10 % means that the acceptable range is 40-60 %), unless a wider range is justified by a bioequivalence study (decision diagram No. 7 (3));

b) disintegration. For fast-dissolving medicinal products (dissolution > 80 % within 15 minutes at a pH of 1.2, 4.0, and 6.8) containing highly soluble active pharmaceutical substances in the physiological pH range (the dose is dissolved in less than 250 ml of the medium at the pH of 1.2 to 6.8), the dissolution test may be replaced by a disintegration test. A disintegration test is the most appropriate if a relationship with dissolution has been established or it has been shown that the determination of disintegration suits better than a dissolution test. In such cases, a dissolution test may not be required. When choosing dissolution or disintegration tests, it is assumed that information

about the development will be provided to confirm the reliability of the medicinal product composition and manufacturing process (decision diagram No. 7 (1));

c) hardness and/or abrasion tests. If hardness and/or abrasion tests are performed during the medicinal product manufacturing process, these quality indicators do not need to be included in the specification. If hardness and abrasion have a critical impact on the medicinal product quality (for example, chewing tablets), then the relevant tests and acceptance criteria should be included in the specification;

d) dosage uniformity of units (dosage uniformity determined by the mass variation method, and uniformity of dosage determined by the method of uniformity of an active pharmaceutical ingredient content per dosage form unit). Pharmacopoeial procedures must be used for testing. The specification shall includes one of these tests. If applicable, these tests shall be performed during the medicinal product manufacturing process, and the acceptance criteria must be included in the specification. If deviations in the medicinal product mass exceed the threshold value at which homogeneity of the content can be determined by determining the mass deviation, the applicants must make sure that the medicinal product homogeneity is satisfactory during development;

e) water content. When required, a water content test shall be included in the specification. Acceptance criteria can be justified by data on the effect of hydration or water absorption by the medicinal product. In some cases, it is sufficient to use a procedure of determining the mass loss during drying, but it is preferable to use a detection method specific to water (for example, Fischer titration);

f) microbial limits. Microbial limit tests are required to confirm compliance with the Good Manufacturing Practice and to ensure the medicinal

product quality. Such medicinal products tests may not be performed if two conditions are met:

the medicinal product components are tested before the manufacturing starts;

according to the validation studies, there is no significant risk of microbial contamination or proliferation during the medicinal product manufacturing.

These Requirements shall apply to excipients and medicinal products. In both cases, a sample-based approach may be used (if applicable) (decision diagram No. 6).

The specification must include acceptance criteria for the total aerobic microbial count, total yeasts and moulds count, as well as information about the complete absence of certain types of bacteria that are not allowed in the medicinal product (for example, *Staphylococcus aureus, Escherichia coli, Salmonella spp., Pseudomonas aeruginosa).* Microbial limits should be determined using appropriate pharmacopoeial procedures, and the sampling frequency or time points of the production process should be justified by data and experience. When choosing the type of microbial limit tests and acceptance criteria, the nature of the active pharmaceutical ingredient, the manufacturing method and the intended purpose of the medicinal product should be taken into account. Subject to the proper scientific justification of liquid dosage forms for oral administration, it is allowed not to conduct the microbial limit tests. Additional explanations of when microbial tests should be performed are provided in decision diagram No. 8.

Liquid dosage forms for oral administration

41. For liquid dosage forms for oral administration and powders intended for the preparation of liquid dosage forms for oral administration, the following

tests shall be applied:

a) uniformity of dosage units. The concept includes both the dosage uniformity determined by the mass variation method, and the dosage uniformity determined by the method of uniformity of the active pharmaceutical ingredient content in the medicinal product. Pharmacopoeial procedures must be used for testing. The specification usually includes one of these tests, but not both simultaneously. If applicable, these tests shall be performed during the medicinal product manufacturing process, and the acceptance criteria must be included in the specification. This rule shall apply to the medicinal products in both single-dose and multi-dose packages. If deviations in the medicinal product mass exceed the threshold value at which homogeneity of the content can be determined by determining the mass deviation, the applicants must make sure that the medicinal product homogeneity is satisfactory during development.

The dosage unit is the dose taken by the patient per administration. If the actual dose used by the patient is controlled, it can be determined directly or by calculation, i.e. by dividing the total measured mass or volume of the medicinal product by the estimated number of doses. If a dosing device (for example, a medical pipette or a bottle dropper) is a part of the package, this device must be used to determine the dose. Otherwise, one need to use standard volume units. The choice of a dosing device shall be determined during development. For powders intended for dissolution, a homogeneity test is generally considered acceptable;

b) pH. If applicable, the acceptance criteria for the pH range and the rationale for its selection should be provided;

c) microbial limits. Microbial limit tests are required to confirm compliance with the Good Manufacturing Practice and to ensure the medicinal product quality. Such medicinal products tests may not be performed if two

conditions are met:

the medicinal product components are tested before the manufacturing starts;

according to the validation studies, there is no significant risk of microbial contamination or proliferation during the medicinal product manufacturing.

These Requirements shall apply to excipients and medicinal products. In both cases, a sample-based approach may be used (if applicable) (decision diagram No. 6).

The specification must set forth the acceptance criteria for the total aerobic microbial count, total yeasts and moulds count, as well as information about the complete absence of certain types of bacteria that are not allowed in the medicinal product (for example, *Staphylococcus aureus, Escherichia coli, Salmonella spp., Pseudomonas aeruginosa).* Microbial limits should be determined using appropriate pharmacopoeial procedures, and the sampling frequency or time points of the production process should be justified by data and experience. When choosing the type of microbial limit tests and acceptance criteria, the nature of the active pharmaceutical ingredient, the manufacturing method and the intended purpose of the medicinal product should be taken into account. Subject to the proper scientific justification of liquid dosage forms for oral administration, it is allowed not to conduct the microbial limit tests. Additional explanations of when microbial tests should be performed are provided in decision diagram No. 8;

d) antimicrobial preservative content. For oral liquid dosage forms requiring the addition of an antimicrobial preservative, the content acceptance criteria should be established. When selecting the antimicrobial preservative content acceptance criteria, one should be guided by the amount of antimicrobial preservative required to maintain the microbial limits of the

medicinal product at all stages of its use and during the entire shelf life. When using the pharmacopoeial procedures, it is required to prove the efficacy of an antimicrobial preservative against the delay of microorganism growth at the lowest concentration set forth in the specification. The antimicrobial preservative content test must usually be performed during the batch release. In some cases, it may be sufficient to conduct a test during the medicinal product manufacturing process instead of the test at release. If the antimicrobial preservative test is an in-process test, its acceptance criteria should also be included in the specification. Despite the fact that the chemical test for the antimicrobial preservative content is a standard indicator included in the specification, the efficacy of an antimicrobial preservative must be proved during development, scaling, and shelf life (for example, during the stability test described in the decision of the Board of the Eurasian Economic Commission dated May 10, 2018 No. 69 On approval of Requirements to stability studies of medicinal products and pharmaceutical substances);

e) antioxidant content. The antioxidant content test must be performed during the batch release. Under certain circumstances, on the basis of the medicinal product development data and the stability testing results, it is allowed to avoid testing at the end of shelf life, and replace the testing at release with the test during the medicinal product manufacturing process (with appropriate justification). If the antioxidant content test is performed during the medicinal product manufacturing process, the acceptance criteria should be included in the specification. If the antioxidant content test is performed exclusively at release, when the packaging (closure) process or system are amended, a second test should be performed to apply this approach;

f) extractable substances. If the data obtained during the development and stability tests of an active pharmaceutical ingredient and/or medicinal product indicate that the content of substances extracted from the packaging

(closure) system is consistently below the levels that are acceptable and safe, then it is allowed to exclude the test for their content from the specification. If changes are made to the packaging (closure) system or to the medicinal product composition, this approach should be reviewed. If the data indicate that it is required to conduct tests and include the acceptance criteria for substances extracted from components of the packaging (closure) system (for example, from rubber stoppers, gaskets in the cap, plastic vials, etc.), then for the medicinal products, the primary packaging of which is not made of glass or placed in glass vials with capping elements not made of glass, it is advisable to conduct tests for extracted substances and establish the acceptance criteria for these tests. It is required to list the components of the packaging (closure) system and provide data on these components, starting from the earliest development stage;

g) alcohol content. Where, in accordance with the Requirements for labeling medicinal products for human and veterinary use, approved by the Decision of the Council of the Eurasian Economic Commission dated November 3, 2016 No. 76, the information about the alcohol content shall be specified on the label, then it must be included in the specification. The alcohol content shall be determined by direct quantitation or calculation method;

h) dissolution. For oral suspensions and dry powdered medicinal products to be resuspended, in addition to the quality indicators described above, it is advisable to include a dissolution test and acceptance criteria in the specification (for example, for insoluble active pharmaceutical ingredients). The dissolution test should be performed at the batch release. If there are justifications obtained during the medicinal product development, the test can be performed during the medicinal product manufacturing. Testing devices, environment, and the test conditions should be pharmacopoeial; otherwise, one will need to provide a relevant rationale. Dissolution procedures using the

pharmacopoeial or non-pharmacopoeial conditions and devices must be validated.

For immediate-release dosage forms, "single-point" determinations are usually sufficient. For modified-release dosage forms, sampling should be performed at multiple points at the appropriate time intervals. The acceptance criteria should be established based on the observed range of deviations, and the dissolution profiles of the batches that were found acceptable *in vivo* should be taken into account. When choosing between the dissolution test and the particle size distribution test, the data obtained during development must be taken into account;

h) particle size distribution. The specification should include quantitative acceptance criteria and procedures to determine the particle size. When choosing between the dissolution test and the particle size distribution test, the data obtained during development must be taken into account; The particle size distribution test should be performed at release. If there are justifications in the form of the data obtained during the medicinal product development, the test can be performed during the medicinal product manufacturing. If it is proven during development that a medicinal product is consistently characterized by rapid release of an active pharmaceutical ingredient, then the exclusion of the particle size distribution test from the specification may be considered.

In the presence of a justification, the dissolution test may be replaced by a particle size distribution test. Acceptance criteria should include the particle size distribution, which is expressed as the percentage of particles that have a size in a given range of the total number of particles. The limits for the average, upper, and/or lower particle size should be clearly set.

Acceptance criteria should be established based on the observed deviation range. In this case, the dissolution profiles of the batches that were acceptable in vivo according to the research findings, as well as the intended

use of the medicinal product, should be taken into account. During development, it is required to consider the possibility of increasing the particles size. The findings of this research should be taken into account when selecting the acceptance criteria;

i) resuspendability. For suspensions characterized by settling of dispersed phase particles during storage (sedimentation), it is advisable to establish the acceptance criteria for resuspendability. Stirring can be a suitable procedure. The specification shall set forth the testing procedure (mechanical or manual). The time required for resuspending when using this procedure should be clearly defined. The data obtained during the medicinal product development may be sufficient to justify the possibility of conducting sample batch tests or excluding this indicator from the specification;

l) rheological properties. For relatively viscous solutions and suspensions, it is advisable to include the rheological property (viscosity, specific density) tests in the specification. The testing procedure and the acceptance criteria must be specified. The data obtained during the medicinal product development are sufficient to justify the possibility of conducting sample batch tests or excluding this indicator from the specification;

m) recovery time. For dry powdered medicinal products intended for dilution before use, the acceptance criteria for recovery time must be specified. It is required to justify the choice of the solvent. The data obtained during the medicinal product development are sufficient to justify the possibility of conducting sample batch tests or excluding this indicator from the specification;

n) water content. For oral medicinal products intended for dilution, if applicable, specify the procedure and criteria for acceptable water content. If the effect of absorbed moisture and hydrated water is well characterized during the medicinal product development, it shall be considered sufficient to conduct

a test for loss on drying. One should use a detection procedure that is specific for water (e.g., Fisher titration).

Medicinal products for parenteral administration

42. The following tests shall apply to the medicinal products for parenteral administration:

a) uniformity of dosage units. The conditions for including the test in the specification are given in the first item of subparagraph "a" of paragraph 41 hereof. For recovery powders that do not contain other added active pharmaceutical ingredients and excipients, as well as for multicomponent recovery powders obtained from true solutions lyophilized in the final container, a mass uniformity test shall be considered acceptable;

b) pH. If applicable, the pH acceptance criteria must be presented and the proposed range must be justified;

c) sterility. For all parenteral medicinal products, a test procedure and an acceptance criterion must be included to assess the sterility. If the data obtained in the course of development and validation justify the release by parameters, this approach can be proposed for medicinal products undergoing the terminal (final) sterilization;

d) bacterial endotoxins (pyrogenes). The specification should include a test procedure and acceptance criteria for bacterial endotoxins, using the procedure involving the lymulus amebocyte lysate (LAL test). When there are justifications, the endotoxin test may be replaced by a pyrogenicity test;

e) mechanical impurities. Appropriate acceptance criteria for mechanical impurities should be provided for the parenteral medicinal products. These include the acceptance criteria for visible particles, solution transparency, and, when required, for invisible particles;

f) water content. For non-aqueous parenteral medicinal products and

parenteral medicinal products requiring recovery, the analytical procedure and the acceptance criteria for the water content as listed in subparagraph "n" of paragraph 41 hereof should be specified;

g) antimicrobial preservative content. The conditions for including the test in the specification are given in subparagraph "d" of paragraph 41 hereof;

h) content of antioxidants (antioxidant preservatives). The conditions for including the test in the specification are given in subparagraph "e" of paragraph 41 hereof;

h) extractable substances. The conditions for including the test in the specification are given in subparagraph "f" of paragraph 41 hereof;

k) testing of functional characteristics of the delivery systems. Parenteral dosage forms packed into pre-filled syringes, autoinjector cartridges or their equivalents must be tested with appropriate acceptance criteria for the functional characteristics of the delivery system. These include the needle patency control, pressure and tightness of the closure (leakage), and/or parameters such as the force to remove the screw cap, the force to move the piston, and the force to actuate the injector. Under certain circumstances, these tests may be performed during the medicinal product manufacturing process. The data obtained during medicinal product development are sufficient to justify the possibility of conducting sample batch tests or excluding some or all characteristics from the specification;

l) osmolarity. If the medicinal product label indicates its tonicity, proper osmolarity control must be performed. The data obtained during medicinal product development and validation may be sufficient to justify conducting this test in the course of the medicinal product manufacturing, random batch tests, or determination of this indicator by calculation;

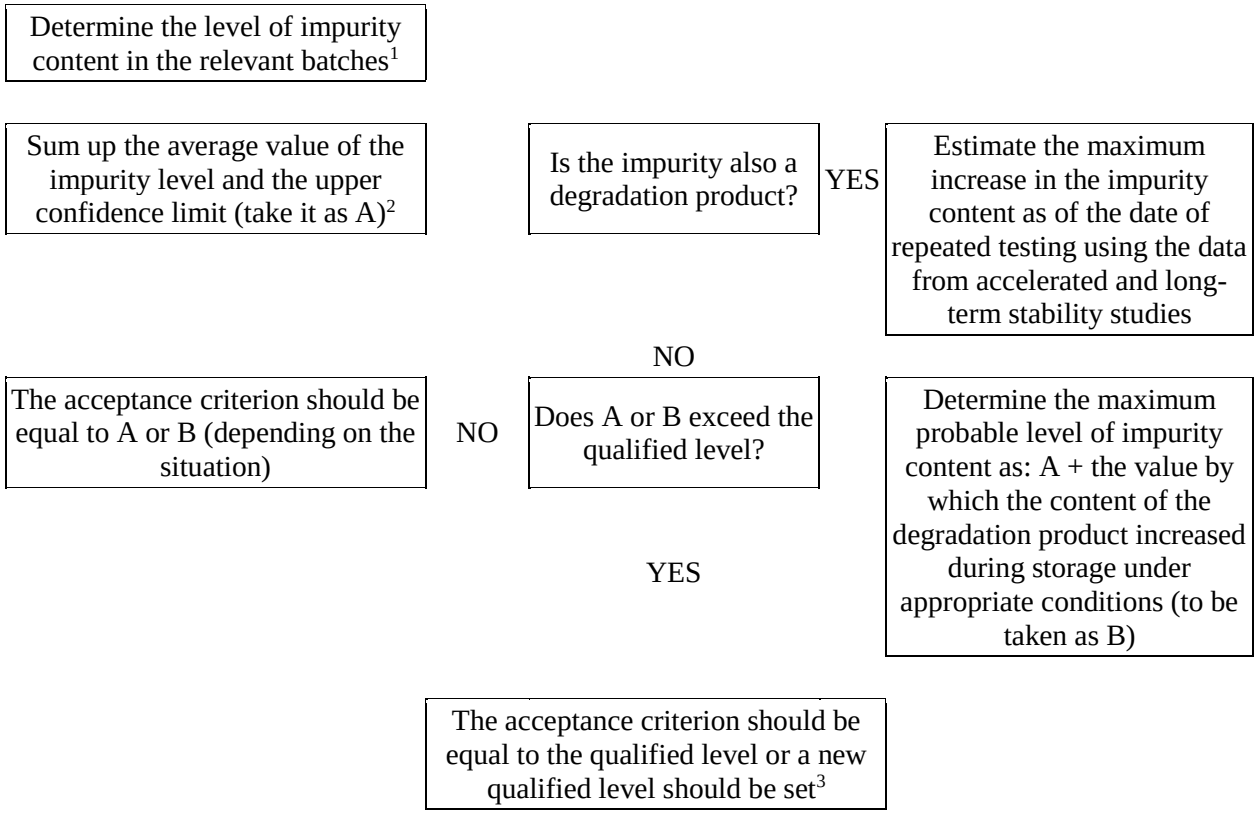
m) particle size distribution. The conditions for including the test in the specification are given in subparagraph "i" of paragraph 41 hereof;

n) resuspendability. The conditions for including the test in the specification are given in subparagraph "k" of paragraph 41 hereof;

o) recovery time. The conditions for including the test in the specification are given in subparagraph "m" of paragraph 41 hereof.

Decision diagram No. 1

Establishment of an acceptance criterion for a controlled impurity in an active pharmaceutical ingredient



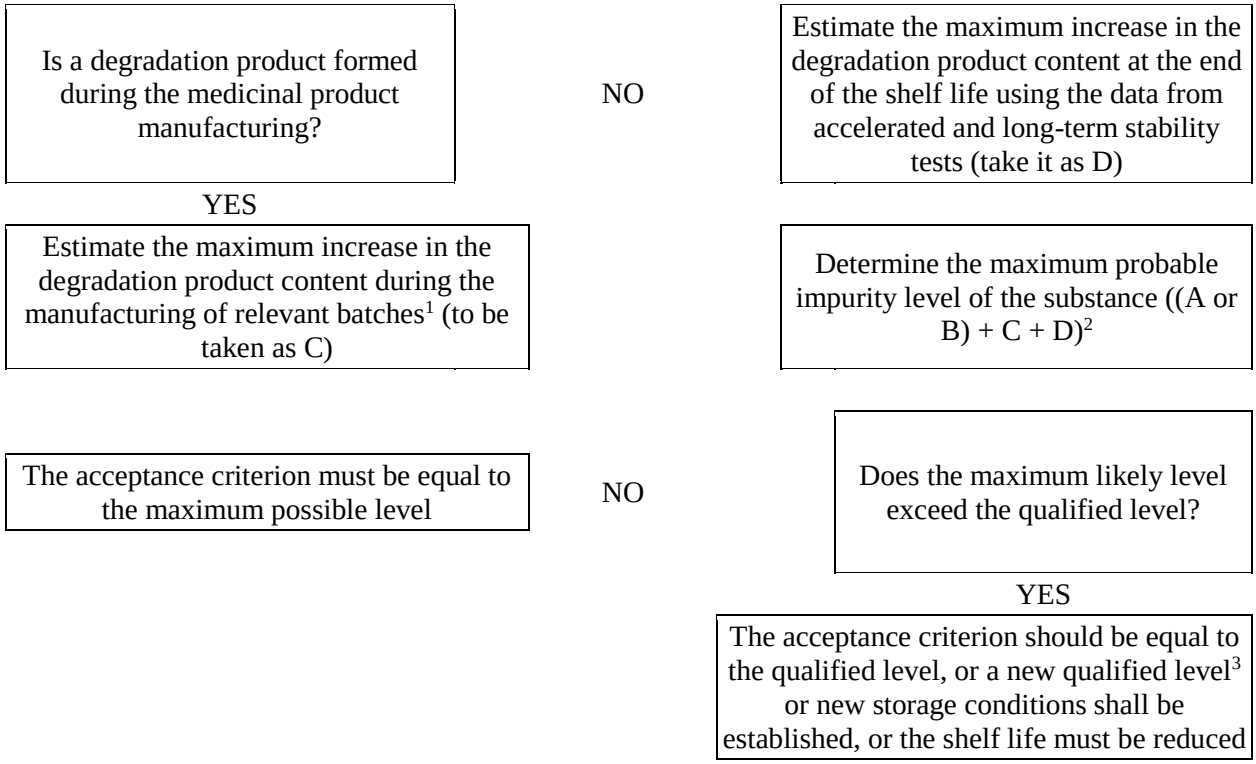
[1] Relevant batches are the batches obtained in the course of research at the stages of development, pilot, and industrial production.

[2] The upper confidence limit is equal to the standard deviation of the batch analysis results multiplied by 3.

[3] It shall be determined in accordance with the rules for the study of impurities in medicinal products and the establishment of requirements for them in the specifications approved by the Commission.

Decision diagram No. 2

Establishment of an acceptance criterion for a degradation product in the medicinal product



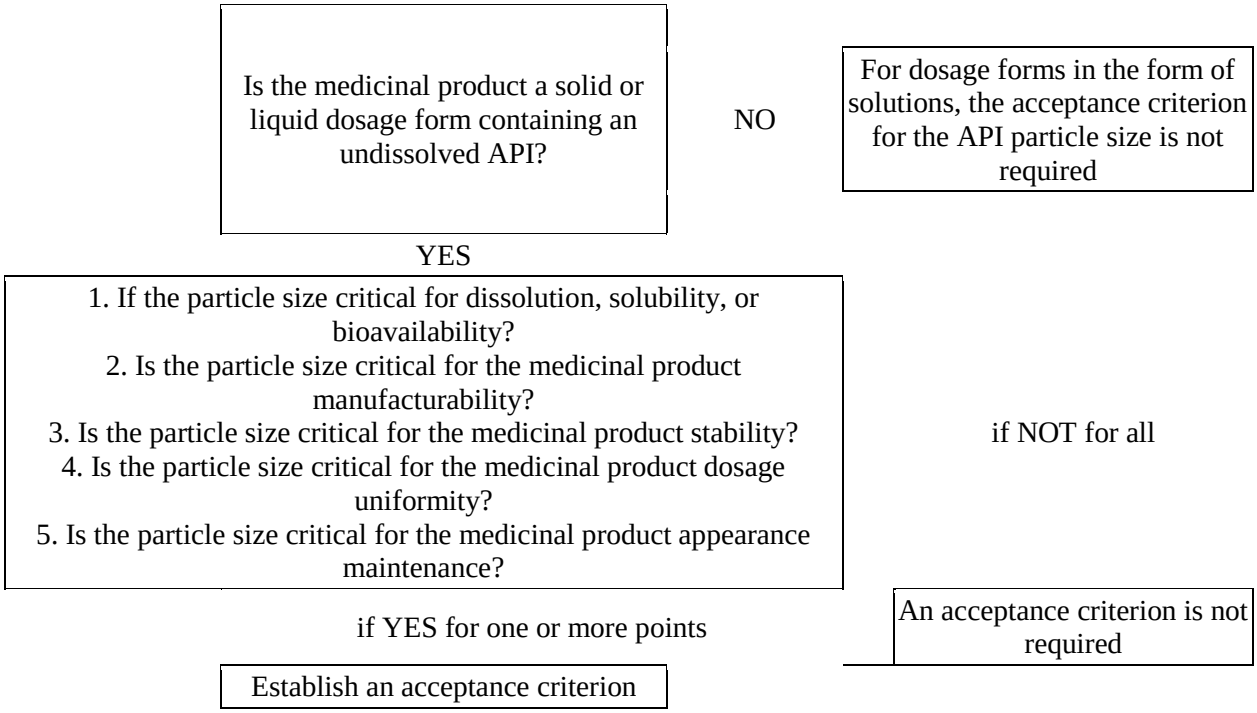
[1] Relevant batches are the batches obtained in the course of research at the stages of development, pilot, and industrial production.

[2] The procedure of determining A and B is presented in the decision diagram No. 1.

[3] It shall be determined in accordance with the rules for the study of impurities in medicinal products and the establishment of requirements for them in the specifications approved by the Commission.

Decision diagram No. 3

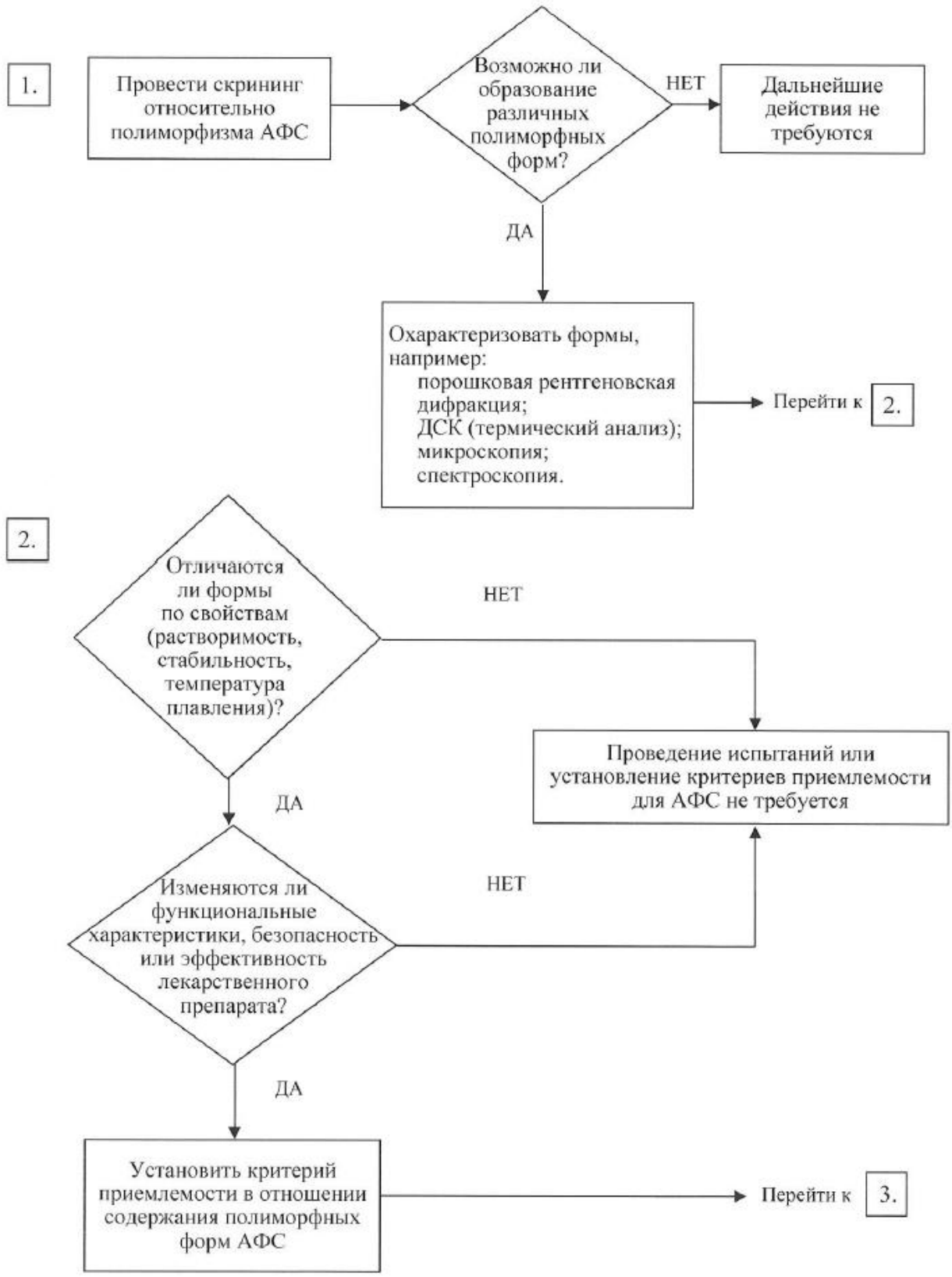
Establishment of the acceptance criteria for the particle size of an active pharmaceutical ingredient (API)



Decision diagram No. 4

Determination of the need to introduce the acceptance criteria for polymorphism of the active pharmaceutical ingredients (APIs) and medicinal products

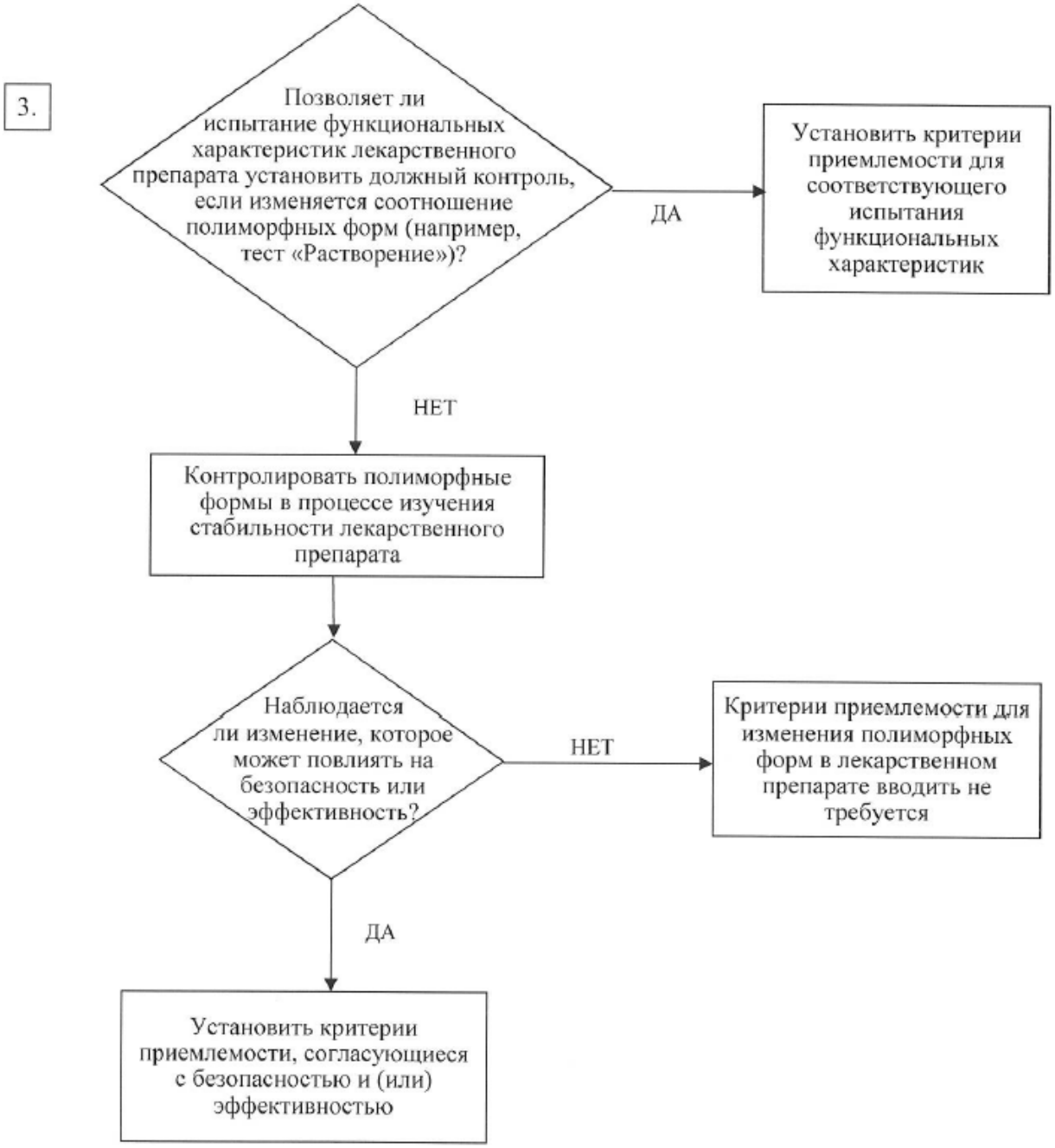
Active pharmaceutical ingredient



To hold a screening of API polymorphism	
Can different polymorphic forms be produced?	
NO	
YES	
No further action is required	

Describe the forms, for example: powder x-ray diffraction; DSC (thermal analysis); microscopy; spectroscopy.	
Go to 2.	
Do the forms have different properties (solubility, stability, melting point)?	
Testing or establishing the acceptance criteria for an API is not required	
Do the functional characteristics, safety, or efficacy of the medicinal product change?	
Establish an acceptance criterion for the content of API polymorphic forms	
Go to 3.	

The medicinal product in the form of a solid or liquid dosage form containing an undissolved active pharmaceutical ingredient if it is technically possible to measure the content of polymorphic forms in the medicinal product



Does the testing of functional characteristics of a medicinal product allow for proper control if the ratio of polymorphic forms changes (for example, the dissolution test)?	
Establish the acceptance criteria for the relevant functional performance test	
YES	
NO	
Control the polymorphic forms in the course of the medicinal product stability study	
Is there a change that could affect the safety or	

efficacy?	
The acceptance criteria do not need to be introduced for change of the medicinal product polymorphic forms	
Establish the acceptance criteria consistent with safety and/or efficacy	

Decision diagram No. 5

Inclusion of procedures for identification, quantitation, and determination of enantiomers, that are impurities for chiral active pharmaceutical ingredients (API) and medicinal products containing the chiral active pharmaceutical ingredients into the specification

Determine the need for verification of chiral API identification at release and/or acceptance tests	
YES AND RACEMATE	
Is the API chiral[1]?	
NO	
Procedures for identification, quantitation, and testing for impurity tests are specific to chiral API are not required YES AND ENANTIOMER	
Include the following in the API specification[2]: identification[3]; quantitation[4]; tests for enantiomer-impurity[5]. Include the following in the medicinal product specification[6]: quantitation[4]; tests for enantiomer-impurity[3].	

[1] Chiral substances of natural origin are out of the scope of these Guidelines.

“As with the other impurities originating from the feedstock used in the synthesis of active pharmaceutical ingredients, the quality control of chiral substances should be provided to set the limits for the corresponding feedstock or intermediate products, if this is justified by the results of research conducted during development. These are mainly cases when there are several chiral

centers (for example, 3 or more), or the control is appropriate at the stage preceding the synthesis of the final active pharmaceutical ingredient.

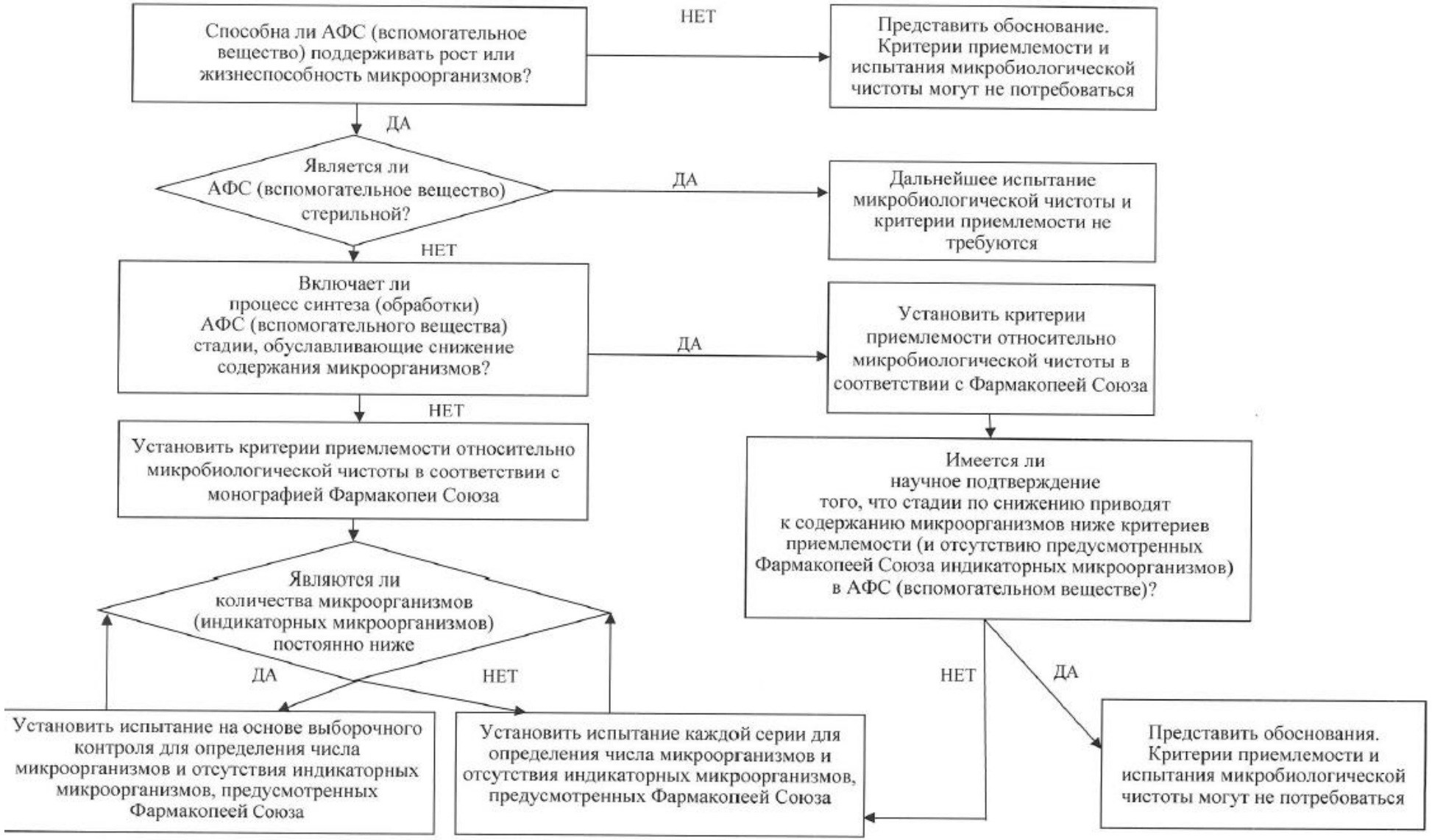
[3] Instead of the chiral compound identification procedure, a quantitation procedure specific to the chiral compound or a test procedure for enantiomers-impurities can be applied.

[4] Instead of the quantitation procedure specific to the chiral compound, a quantitation procedure that is non-specific to the chiral compound can be used in combination with the procedure of controlling the opposite enantiomer.

[5] The content of the opposite enantiomer in the active pharmaceutical ingredient can be determined based on the data obtained using a quantitation procedure specific to the chiral compound, or using a separate procedure.

[6] Medicinal product tests specific to stereoisomers may not be performed if it is shown that racemization during the medicinal product manufacturing process and during the storage of the finished dosage form is insignificant.

Decision diagram No. 6
The indicators of microbial limits of the active pharmaceutical ingredients (API) and excipients

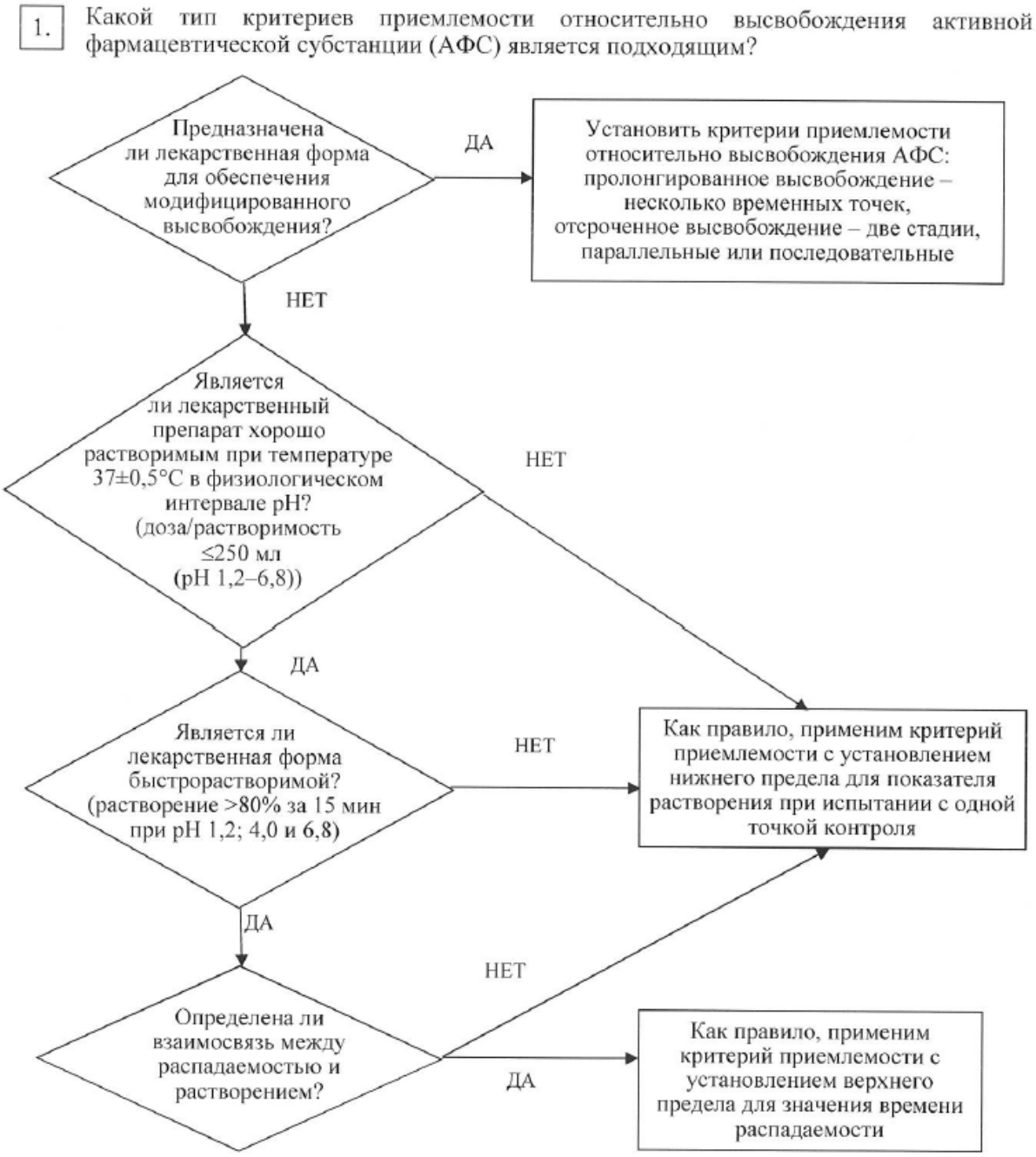


Is the API (excipient) able to support the growth or viability of	

microorganisms?	
NO	
YES	
Submit a justification.	
The acceptance criteria and microbial limit tests may not be required	
Is the API (excipient) sterile?	
Does the process of API (excipient) synthesis (processing) include the stages that cause a decrease in the content of microorganisms?	
Establish the acceptance criteria for microbial limits in accordance with the monograph of the Union Pharmacopoeia	
Are the numbers of microorganisms (indicator microorganisms) constantly lower	
Establish a test based on selective control to determine the number of microorganisms and the absence of indicator microorganisms provided for in the Union Pharmacopoeia	
Establish a test for each batch to determine the microorganism count and the absence of indicator microorganisms provided for in the Union Pharmacopoeia	
The further microbial limit testing and acceptance criteria are not required	
Establish the acceptance criteria for microbial limits in accordance with the Union Pharmacopoeia	
Is there scientific evidence that the reduction steps lead to the microorganism count below the acceptance criteria (and the absence of the indicator microorganisms provided for by the Union Pharmacopoeia) in the API (excipient)?	
Submit the justifications. The acceptance criteria and microbial limit tests may not be required	

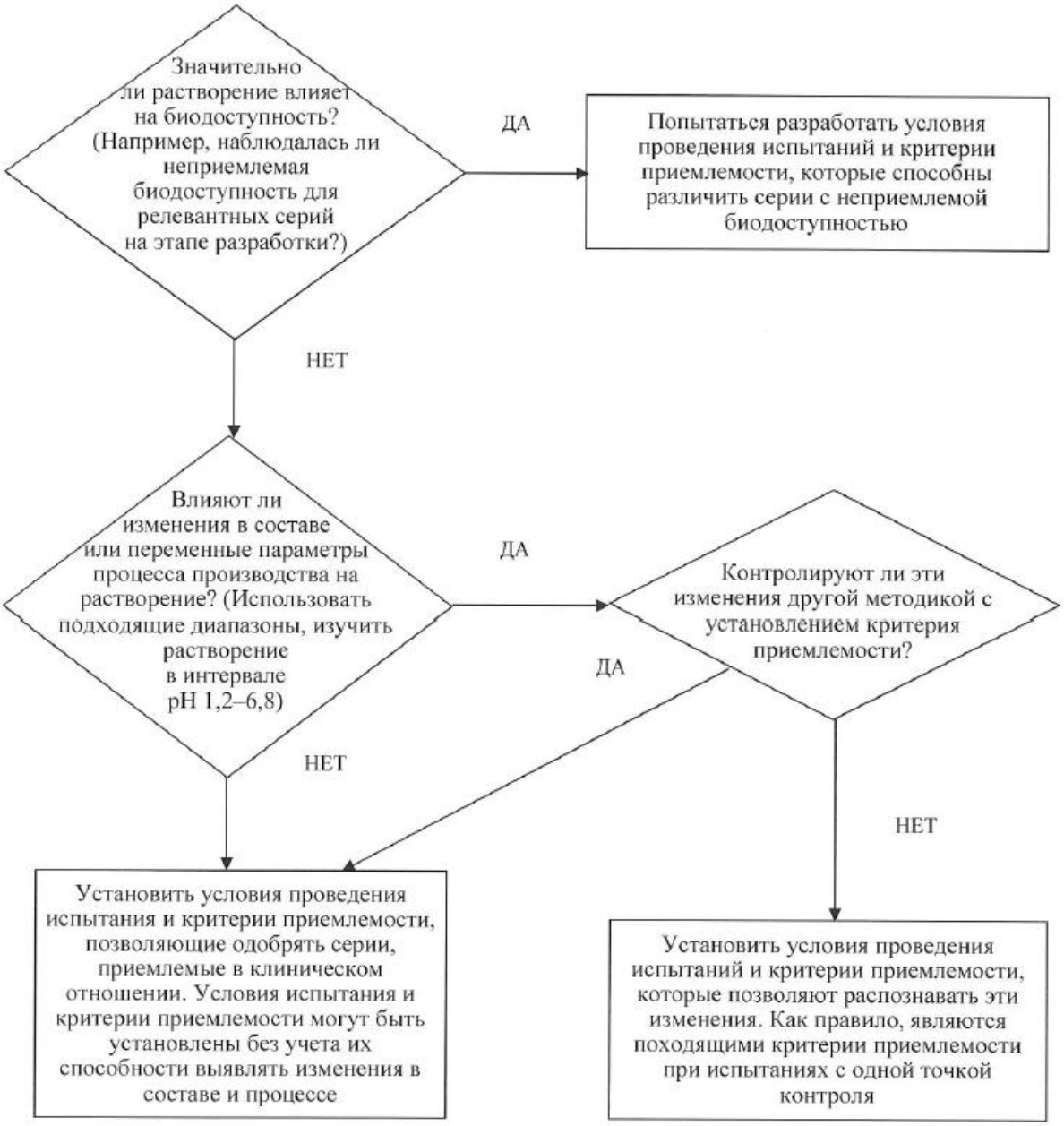
Decision diagram No. 7

Establishment of the acceptance criteria for the medicinal product dissolution test



1. What type of acceptance criteria for the release of an active pharmaceutical ingredient (API) is appropriate?	
Is the dosage form intended to provide a modified release?	
YES	
Establish the acceptance criteria for the API release: prolonged release - multiple time points, delayed	

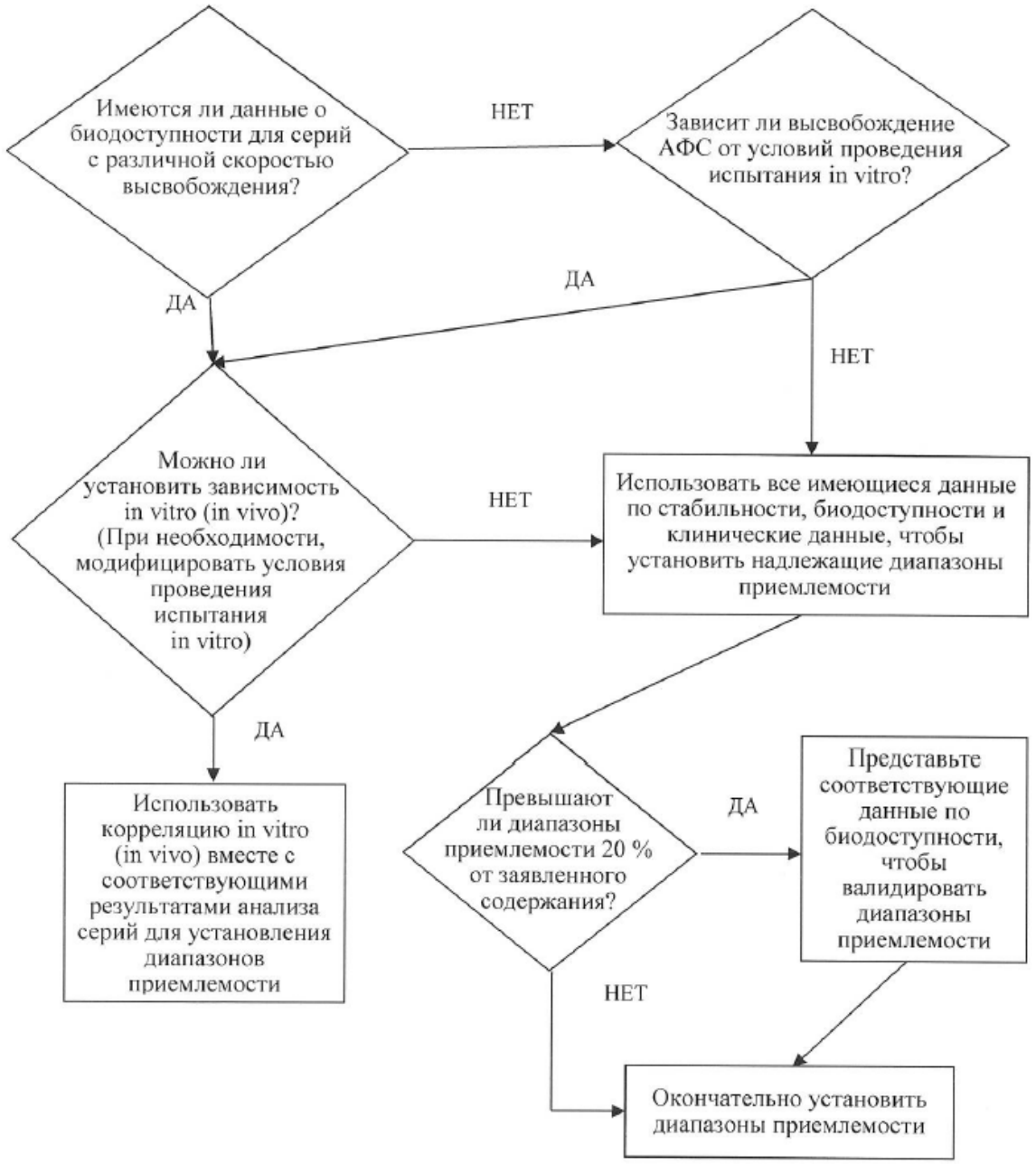
release - two stages, parallel or sequential	
NO	
Is the medicinal product highly soluble at 37±0.5 °C in the physiological pH range? (dose/solubility ≤250 ml (pH 1.2-6.8))	
Is the dosage form fast-soluble? (dissolution >80 % within 15 min at pH 1.2; 4.0 and 6.8)′	
As a rule, the acceptance criterion is applicable when the lower limit for the rate of dissolution is established if the test involves a single point of control	
Is the relationship between disintegration and dissolution determined?	
As a rule, an acceptance criterion with an upper limit for the disintegration time value is applicable	



2. What specific testing conditions and acceptance criteria are appropriate? (immediate release)	
Does the dissolution significantly affect bioavailability? (For example, was there unacceptable bioavailability for relevant batches at the development stage?)	
YES	
Try to develop the test conditions and acceptance criteria that can identify the batches with unacceptable bioavailability	
NO	
Do the changes in the composition or variable parameters of the manufacturing process affect the dissolution? (Use the appropriate ranges, study the dissolution in the pH interval of 1.2 to 6.8)	
Are these changes controlled by a different procedure with an acceptance criterion	

establishment?	
Establish the test conditions and acceptance criteria that allow approval of the clinically acceptable batches. Test conditions and acceptance criteria may be set without regard to their ability to detect changes in the composition and process	
Establish the test conditions and acceptance criteria that allow these changes to be recognized. Generally, the acceptance criteria for tests with a single control point are suitable	

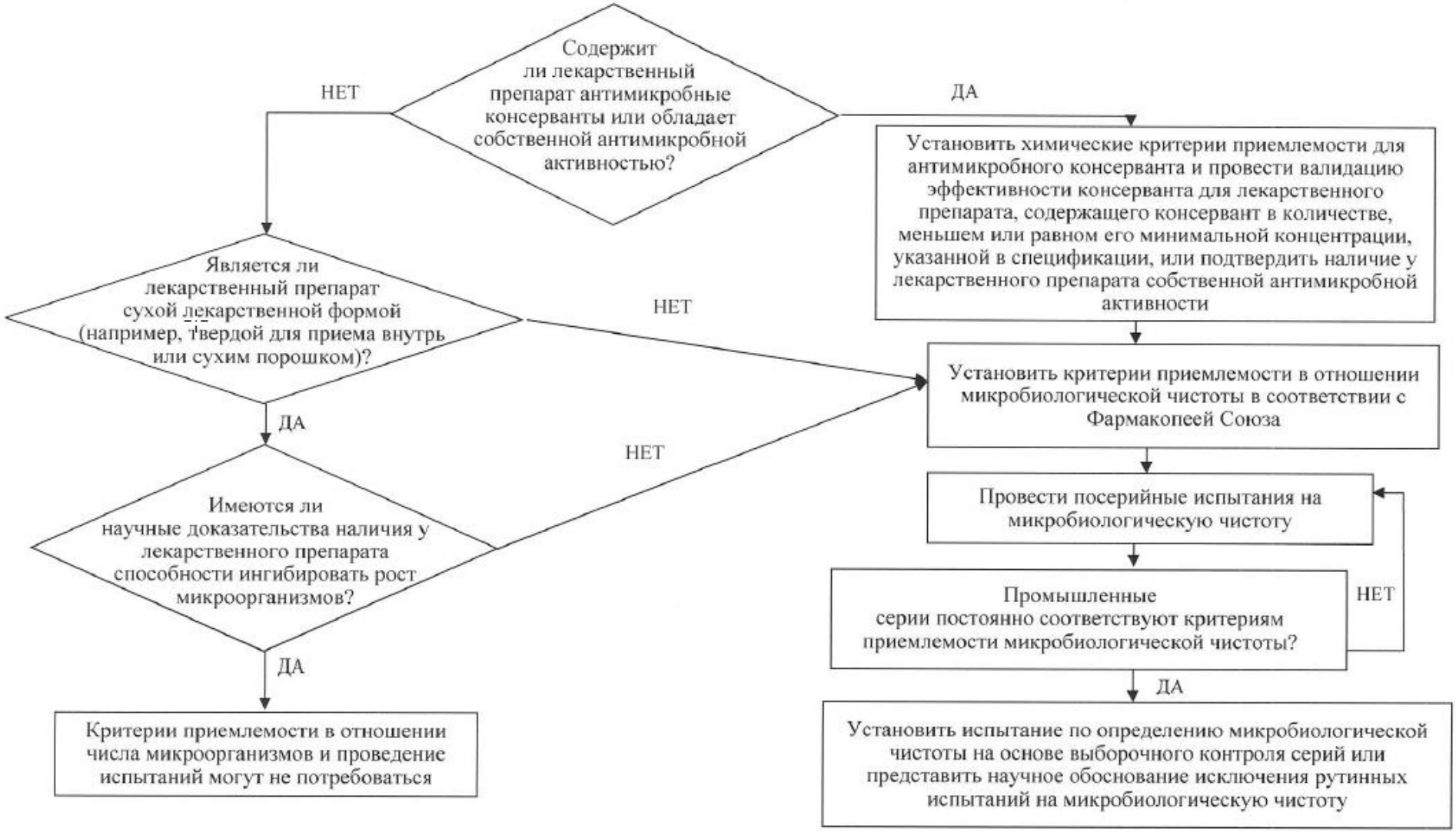
3. Какие диапазоны приемлемости являются подходящими? (пролонгированное высвобождение)



3. What acceptability range are appropriate? (prolonged release)	
Are the bioavailability data available for batches with different release rates?	
NO	
Does the API release depend on the conditions of the in vitro test?	
Y	
Is it possible to establish the dependence in vitro (in vivo)?	
(When required, modify the in vitro test conditions)	
Use all available stability, bioavailability, and clinical data to establish an appropriate acceptability range	

Use in vitro (in vivo) correlation together with the corresponding batch analysis results to establish the acceptability ranges	
Do the acceptability ranges exceed 20 % of the declared content?	
Provide relevant bioavailability data to validate the acceptability ranges	
Finally set the acceptability ranges	

Decision diagram No. 8
Non-sterile medicinal product microbial limit indicators



Does the medicinal product contain antimicrobial preservatives or has its own antimicrobial activity?	
YES	
Establish the chemical acceptance criteria for an antimicrobial preservative and validate the effectiveness of the preservative for a medicinal product containing the preservative in the amount less than or equal to its minimum concentration indicated in the specification, or confirm that the medicinal product has its own antimicrobial activity	
Establish the acceptance criteria for microbial limits in accordance with the Union Pharmacopoeia	
Perform batch tests for microbial limits	
Industrial batches constantly meet the criteria for acceptable microbial limits?	
Establish a test to determine the microbial limits based on the random control of the batches or provide scientific justification to exclude the routine tests for microbial limits	
NO	
Is the medicinal product a dry dosage form (for example, a solid medicinal product for oral administration or a dry powder)?	
Is there a scientific evidence that the medicinal product is able to inhibit the microbial growth?	
The acceptance criteria for the microbial count and testing may not be required	

ANNEX 2

to the Guidelines
for preparation of the normative
document on the medicinal product
quality

(form)

TITLE page
of the normative document

AGREED
_____
(name of the authorised authority of the state of recognition)
_____
_____
(full name, title, signature)

_____ 20___

L.S.

APPROVED
(name of the authorised authority of the reference state)
_____
_____
(full name, title, signature)

_____ 20___

L.S.

AGREED
_____
(name of the applicant or an authorised legal entity)
_____
_____
(full name, title, signature)

_____ 20___

L.S.

NORMATIVE DOCUMENT

Brand name of a medicinal product: _____

International non-proprietary name: _____
(in its absence – the common name, and in the absence of the latter – the chemical name)

Dosage form: _____

Strength: _____

Marketing authorisation holder: _____
(name and country of the marketing authorisation holder)

Number and date of the normative document: _____
(number and date of the certificate of marketing authorisation issued by the reference Member State)