ANNEX

to Recommendation No.
of the Eurasian Economic Commission's Board
dated , 20

GUIDELINES
on Assessing the Quality of Medicinal Products Based on Combinations of Herbal Substances/Herbal Preparations

I. General Provisions

1. These Guidelines shall apply to herbal medicinal products based on combinations of herbal substances and/or herbal preparations.

2. These Guidelines address approaches to the identification and assay of medicinal products based on combinations of herbal substances/herbal preparations, and namely medicinal products containing cut or powdered herbal substances, tinctures, extracts, elixirs, etc., taking into account the complex composition of biologically active herbal substances.

3. These Guidelines are intended for use by applicants when drawing up a specification or a regulatory document on quality, as well as for expert assessment during the procedures of registration, registration confirmation (re-registration), and amendment in case of circulation of the above category of medicinal products in the territory of the Eurasian Economic Union.

4. For the purposes hereof, the term "species" is used having the meaning as defined in the Pharmacopoeia of the Union.

II. Procedure for Drawing Up a Regulatory Document on Quality

5. The general instructions for drawing up a regulatory document on quality supporting the application for registration, registration confirmation (re-registration), or amendment of the pharmaceutical marketing authorization application are set out in Annex No. 3 to the Rules for Registration and Expert Examination of Medicines for Human Use approved by Decision No. 78 of the Eurasian Economic Commission's Council dated November 3, 2016.

6. Medicinal products based on combinations of herbal substances/herbal preparations may contain more than one main group of biologically active substances, i.e. represent their complex mixture, which causes certain difficulties when trying to assess the drug quality by individual biologically active substances. The composition of biologically active substances belonging to an individual group depends, as a rule, on the soil and climate conditions of their habitat. In addition, in some cases, constituents responsible for therapeutic activity in the composition of medicinal products based on combinations of herbal substances/herbal preparations are unknown or only partially identified. The above circumstance justifies the use of active and/or analytical markers for assessing the quality (establishing characteristics) of these medicinal products.

7. The quality control of medicinal products based on combinations of herbal substances/herbal preparations may be complicated by the specifics of the production technology. For example, the manufacture of multicomponent drugs from pharmaceutical substances, each being an extract, has two process flows. One is based on the separate extraction of herbal substances using selective extraction solvents to obtain the necessary herbal preparation;

second is based on the joint extraction of herbal substances from multiple medicinal plants. Moreover, this all may hamper marker detection because of other coextractable biologically active substances of pharmaceutical constituents.

8. The quality of combination herbal medicinal products shall, in general, be ensured and confirmed in accordance with the applicable pharmacopoeial standards regulating the quality of medicinal products, taking into account requirements of the monographs of the Pharmacopoeia of the Union or pharmacopoeias of the Union Member States in the absence of the relevant monographs in the Pharmacopoeia of the Union, as well as in accordance with the legislation of the Member States of the Eurasian Economic Union (hereinafter, Member States). Medicinal products shall be tested by all relevant quality indicators. The identification and assay of each pharmaceutical substance (herbal substance and/or herbal preparation) contained in medicinal products is required. These tests shall ensure the objective assessment of the quality of herbal medicinal products during the stability study.

9. These Guidelines shall apply with account of the need to use analytical methods for the identification and assay of the herbal substance and/or the herbal preparation as provided in the particular monographs of the Pharmacopoeia of the Union or, in the absence thereof, in monographs of pharmacopoeias of the Member States. The applicant shall justify each adopted approach, taking into account the combined nature of the declared herbal medicinal product.

10. If there is no possibility to perform identification and assay of some active constituents in the composition of the herbal medicinal product or its quality assessment by the specified characteristics during storage, alternative approaches may be used (validation of the manufacturing process;

confirmed identification of a pharmaceutical substance (herbal substance and/or herbal preparation) immediately before its use in the production process). Testing shall not be waived as the quality of combination herbal medicinal products shall be comparable to that of monocomponent (herbal) medicinal products. In these instances, applicants should seek specialized scientific advice in accordance with paragraph 26 of the Rules for Registration and Expert Examination of Medicines for Human Use. The production process should be planned so that the manufacture of the herbal medicinal product is controlled at all stages and its composition conforms with the declared composition. The manufacturing process design should be supported by well-documented process validation. The relevant in-process testing program (e.g. tests at different time points in case of stepwise addition of herbal substances and/or herbal preparations) and the identification of the herbal substance and/or the herbal preparation immediately before its introduction into the manufacturing process of the herbal medicinal product are measures to ensure the consistency of the quality and declared composition of the herbal medicinal product. Each manufacturing process step should be considered as critical. Therefore, routine control shall provide for the relevant procedures to ensure the correct use of the herbal substance (herbal preparation) and/or excipients. Production process and validation data should be provided as part of both the full and simplified marketing authorization application of the herbal medicinal product.

11. In case of joint assay of constituents, the specification for the herbal substance (herbal preparation) shall provide for the maximum content of the common marker (additional marker if it differs from the specific marker) to guarantee its detection in the herbal medicinal product.

12. If applicable, the same principles shall apply to control testing performed at the intermediate step in the manufacturing process of the herbal medicinal product.

13. The regulatory document on quality shall include a specification (in accordance with Module 3 Section 3.2.P.5.1 of marketing authorization application) with the list of all quality indicators, standards (acceptable limits), and references to test methods.

14. The identification and assay of each herbal substance in the combination herbal medicinal product shall be subject to the following requirements:

1. Identification

15. Quality indicators shall be determined in accordance with the requirements of the general monograph of the Pharmacopoeia of the Union or, in the absence thereof, in accordance with requirements of general monographs of pharmacopoeias of the Member States on dosage forms, taking into account their specifics and the nature of the pharmaceutical substance in accordance with the requirements of the particular pharmacopoeial monograph. Names of quality indicators shall be set out in the specification in accordance with the general monograph of the Pharmacopoeia of the Union or, in the absence therein, in accordance with general monographs of pharmacopoeias of the Member States. If any test for individual indicators is performed selectively or with an established frequency, the specification shall point out the test selectivity and frequency.

Multicomponent drugs based on herbal preparations (whole herbal substances; cut herbal substances and/or powder; species)

16. After the selection of samples for testing species (whole, cut, and/or powdered) according to the relevant general monographs of the

Pharmacopoeia of the Union or, in the absence thereof, in accordance with the relevant monographs of pharmacopoeias of the Member States, the analytical sample shall undergo a visual inspection, whereby it is necessary to describe the general appearance of the species, note the correspondence of the observed color and smell (if any), and afterwards provide the description of morphological characteristics of individual herbal preparations contained in the medicinal product (with the naked eye or using a hand lens and a stereomicroscope) to confirm their compliance with the requirements of the particular pharmacopoeial monograph of the Union or, in the absence thereof, with particular monographs of pharmacopoeias of the Member States or the regulatory document on quality and specify the particle size of the herbal preparation (test for the External Characteristics quality indicator).

17. It is required to describe the anatomical and diagnostic characteristics of each herbal preparation in the species and provide photos (images) of the main microscopic characteristics (test for the Microscopic Characteristics quality indicator).

18. Apart from tests for External Characteristics and Microscopic Characteristics quality indicators, the identification of herbal preparations being constituents of the species shall be confirmed by tests for the main groups of biologically active substances that determine the therapeutic effect of the extract from the species using the following methods: chemical analysis (qualitative reactions), microchemical and histochemical analysis of the species or its extracts with specification of the name of the test group of biologically active substances, as well as physico-chemical methods of analysis: chromatographic, spectral, etc.

19. The presence of individual constituents in the species shall be confirmed using possibilities of chromatographic methods, including: TLC, HPLC, etc. in aqueous extracts, aqueous alcoholic extracts, or extracts

obtained with the use of other suitable solvents for extracting the test group of biologically active substances using corresponding reference standards or markers (analytical or active).

20. Testing by UV spectrophotometry shall be performed in extracts from the species, if provided for by the requirements of the particular pharmacopoeial monograph of the Union or, in the absence thereof, by particular monographs of pharmacopoeias of the Member States or the regulatory document on quality. In this case, it is necessary to provide the conditions of spectral registration, as well as the wavelengths of the absorption maximum (maxima) and minimum (minima) and/or shoulder.

Drugs Based on Combinations of Herbal Substances/Herbal Preparations (tinctures, extracts, etc.)

21. The identification of constituents with known therapeutic activity or active markers specific to each type of herbal substances and/or herbal preparations in aqueous alcoholic extracts obtained from a mixture of herbal substances or representing a mixture of extracts (aqueous, aqueous alcoholic, alcoholic) shall be performed using the methods of chemical analysis (qualitative reactions) and physico-chemical analysis (chromatography, UV spectrophotometry, etc.) for the main groups of biologically active substances with specification of their names next to the test result. Developing the analytical procedure requires comparison with active constituents specific to the constituents of the species (medicinal herbs mixture) in accordance with Decision Tree No. 1 "Identification of Pharmaceutical Substances in Combination Herbal Medicinal Products" provided in the Annex hereto.

22. If herbal preparations with known therapeutic activity or active markers of medicinal products based on combinations of herbal substances/herbal preparations are not known:

Each herbal preparation that can be identified shall be identified in the finished medicinal product in accordance with the Guidelines on Selection of Tests and Acceptance Criteria for Drawing Up Specifications for Herbal Substances, Herbal Preparations, and Herbal Medicinal Products (Annex to Recommendation No. 6 of the Eurasian Economic Commission's Board dated February 12, 2019) (hereinafter, the Guidelines on Selection of Tests and Acceptance Criteria);

If each herbal preparation cannot be identified in the finished medicinal product, appropriate rationale and documentation (protocol, report) should be provided to confirm that the possibility of using all analytical methods usually applied for identification has been investigated without achieving any positive result.

23. The identification should be performed as an in-process control at the latest point in the manufacturing process of the medicinal product where analysis is still possible. The approach taken should be justified by the applicant.

24. The identification should be supported by documented evidence on the manufacture of the medicinal product batch (batch records) and process validation. In addition, the release specifications of the medicinal product shall include suitable identification methods (e.g. characteristic chromatograms in accordance with the Guidelines on Selection of Tests and Acceptance Criteria).

25. The sum of the identification methods shall allow appropriate characterization of herbal medicinal products based on combinations of herbal substances/herbal preparations.

26. If in-process testing is not possible, identification should be performed in accordance with the specifications immediately before the

introduction of herbal substances in the manufacture of the herbal medicinal product. The approach taken should be justified by the applicant.

27. The identification should be supported by documented evidence on the manufacture of the medicinal product batch (batch records) and process validation. The applicant shall specify and justify which information is submitted in the dossier in order to document quality, and which documentation is available upon inspection by the competent authorities.

28. Moreover, the release specifications of the herbal medicinal product shall include suitable identification methods for pharmaceutical substances in combination herbal medicinal products (e.g. characteristic chromatograms). The sum of the identification methods shall allow appropriate characterization of herbal medicinal products based on combinations of herbal substances/herbal preparations.

2. Assay

29. Developing the analytical procedure requires the correlation of therapeutic activity with the biologically active substances of each pharmaceutical substance in combination herbal medicinal products in accordance with Decision Tree No. 1 "Assay of Pharmaceutical Substances in Combination Herbal Medicinal Products."

30. The Assay section shall include the validated procedure (procedures) for determining an individual substance or a sum of biologically active substances in a specific group of biologically active compounds on an individual substance basis using active markers or analytical markers of herbal medicinal products based on combinations of herbal substances/herbal preparations.

31. The use of markers should be justified. Acceptable methods may include chemical (titrimetry) and physico-chemical methods (different types of chromatography, ultraviolet–visible spectrophotometry, etc.).

32. If constituents with known therapeutic activity or active markers are known, their content in herbal medicinal products based on combinations of herbal substances shall be determined.

33. If constituents with known therapeutic activity or active markers are known but the assay is not possible, determination may be carried out for the total content of biologically active substances of the same groups contained in multiple pharmaceutical substances of the herbal medicinal product.

34. If the assay is difficult to be performed for the medicinal product based on combinations of herbal substances/herbal preparations, appropriate rationale and documentation (protocol, report) that all analytical methods usually applied for this purpose have been investigated shall be provided.

35. Furthermore, an appropriate manufacturing process design supported by well-documented process validation shall ensure that the manufacture and quality of the medicinal product based on combinations of herbal substances/herbal preparations is well-controlled and that the composition of the medicinal product conforms with the declared composition.

36. The manufacturing process development studies (e.g. analytical profiles during the stepwise addition of combinations of herbal substances/herbal preparations) are pivotal in this regard.

37. In addition, it is required to take into account results of preliminary conducted studies assessing the quality of herbal substances during storage, including possible degradation products. All the above shall reinforce the proposed approach to ensuring the quality and composition of the medicinal product, e.g. assay of herbal substances as in-process control. The approach

taken should be justified by the applicant. The adopted approach should be confirmed with documented evidence on the manufacture of the medicinal product batch (batch records).

38. Moreover, release and shelf life specifications of herbal substances/herbal preparations shall include suitable assay methods for the medicinal product based on combinations of herbal substances/herbal preparations in accordance with the Guidelines on Selection of Tests and Acceptance Criteria.

39. Provisions of paragraphs 21-38 shall apply to approaches to the identification and assay of medicinal products based on combinations of herbal substances/herbal preparations.

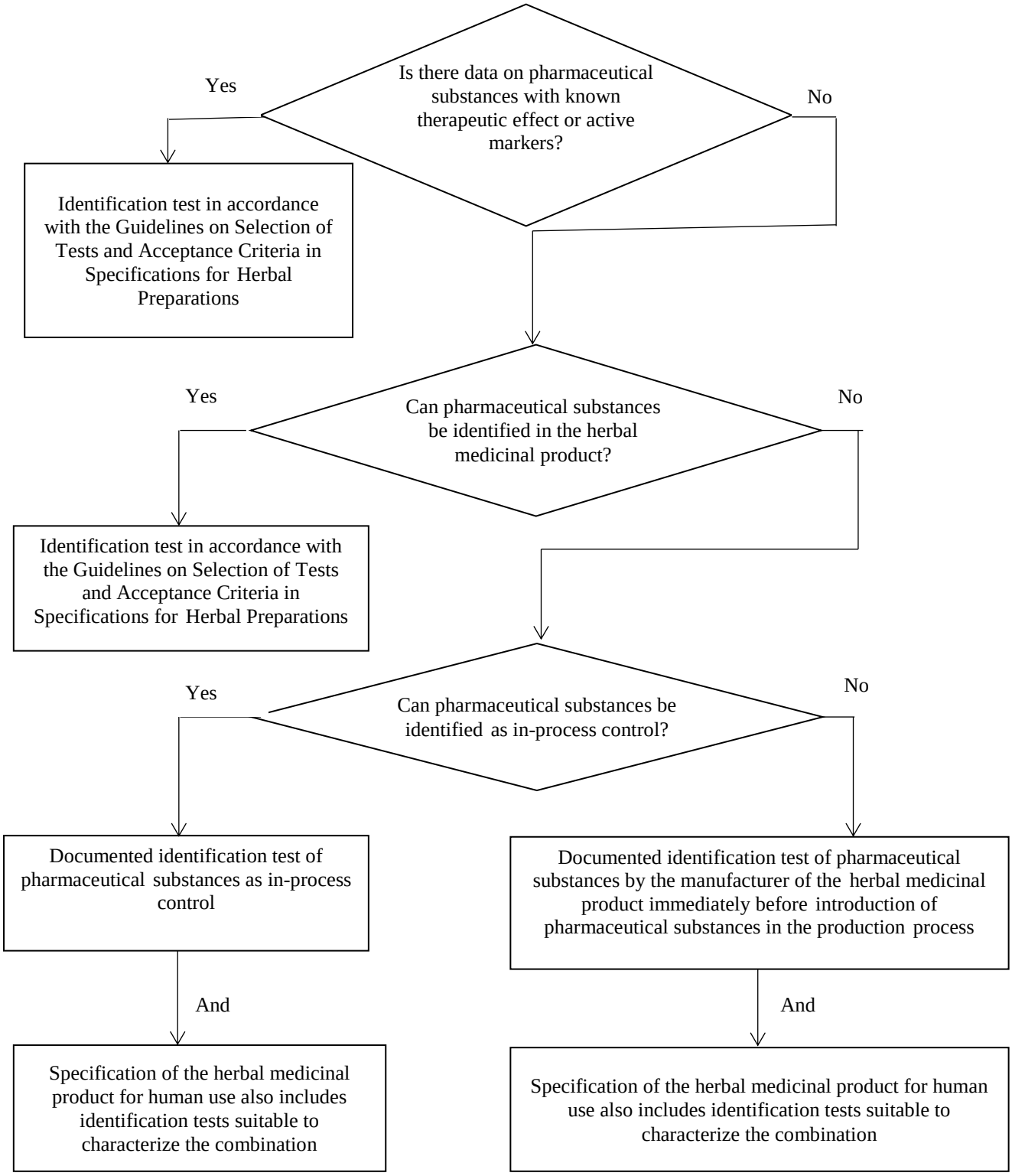
40. Overall release and shelf life specifications for the medicinal products of this group shall therefore be a set of tests that individually enable the identification and determination of the content of biologically active substances in the drug based on combinations of herbal substances/herbal preparations. All other suitable tests shall contribute to the full and explicit evaluation of characteristics of herbal medicinal products.

ANNEX

to the Guidelines on Assessing
the Quality of Medicinal
Products Based on
Combinations of Herbal
Substances/Herbal Preparations

DECISION TREES

Decision Tree No. 1
Identification of Pharmaceutical Substances in Combination Herbal Medicinal Products



Decision Tree No. 2
Assay of Pharmaceutical Substances in Combination Herbal Medicinal Products