INTRODUCTION

To the Recommendation by the Board of
the Eurasian Economic Commission
Dated 20__ No

Herbal Medicines'
QUALITY MANUAL

I. Introduction

1. The Herbal Medicines' Quality Manual (hereinafter referred to as the Quality Manual) relates to preparation of Module Three "Quality" within the dossier submission/new drug application for the herbal medicines in accordance with Annex No 1 «Requirements Applicable to the Regulatory Dossier Submission in the CTD Format» in line with the guidelines for authorisation and evaluation of medicinal products for human use approved by the Decision of the Board of the Eurasian Economic Commission as of 3rd November 2016 No 78 (hereinafter referred to as the Guidelines, as the Commission). The current Quality Manual describes specific considerations relating to the herbal medicines and its differences from the medicinal products that contain pharmaceutical substances with a defined chemical structure. This Quality Manual is inseparably linked with the Specifications Manual: the trials and acceptance criteria for the herbal substances, herbal pharmaceutical substances as well as the herbal medicines i.e. the herbal medicinal products following an abridged regulatory dossier submission (traditional herbal medicinal products).

2. The herbal medicines may additionally contain either vitamins or minerals. This is why in view of the above, this Quality Manual describes approaches focusing on the compounds of the herbal pharmaceutical

substance(-s) with the vitamins and/or minerals. Therefore, both the quality, specifications and documentation for each vitamin/mineral must comply with the effective requirements.

3. The contents of the regulatory dossier must comply with the requirements of the Guidelines along with all the relevant data submission.

II. Scope and Purpose

4. This Quality Manual regulates general quality aspects of the herbal medicines. The medicinal products containing individual components or its blend with clearly defined chemical contents should not be regarded as the herbal medicinal products.

5. This Quality Manual is inseparably linked with Annex No 7 «Requirements for the Herbal Medicines' Manufacturing» and with the rules of the Good Manufacturing Practice of the Eurasian Economic Union approved by the Decision of the Commission Board as of 3rd November 2016 No 77. A sustainable quality of the herbal medicinal products can be ensured in case of a stringent and detailed characterization of the raw materials, in particular if a botanical identification of the consumed herbal materials has been performed. To ensure a sustainable quality of the raw materials, it is necessary to be also aware of its geographic origin and conditions where the relevant herbal raw materials have been collected. It is necessary to be mindful of the good practices for cultivation, harvesting and storage of the herbal raw materials.

III. The Terms and Definitions

6. In this Quality Manual the concepts are used in the following meaning:

a “quantification” is a method of conditioning a herbal pharmaceutical substance to achieve a clearly defined blend composition exclusively by means of blending different lots of the herbal pharmaceutical substances, e.g. the relevant extracts;

“constituents with a known therapeutic activity” – either the substances or a group of substances whose chemical composition is determined and whose contribution into a therapeutic activity of the herbal pharmaceutical raw materials (herbal pharmaceutical substance) or herbal medicinal products is well known;

“acceptance criteria” – numerical limits, range or some other relevant intervals applicable to assess the trials’ outcomes;

“a drug extract ratio (DER)” – a proportion between the volumes of the pharmaceutical herbal raw materials used in production of the herbal pharmaceutical substance and the volumes of the yielded herbal pharmaceutical substance. A number expressed as an actual range and specified before a double point stands for a relative amount of the herbal raw materials whereas a number specified after a double point – a relative amount of the yielded herbal product;

“a herbal medicinal product” – a medicinal product that contains pharmaceutical herbal raw materials and/or the products based on these raw materials as its exclusive inherent active components;

“traditional herbal medicinal products” – medicinal products for human use that comply with the conditions described in Chapter 15.2 in Annex No1 to the Guidelines;

Примечание [PO1]: Additionally in Russian text not present in translation: Medicinal herbal products with a simplified registration dossier

“herbal substances” – either fresh or dried plants, seaweed, mushrooms or lichen or its parts, either in one piece or milled used in pharmaceutical

manufacturing. Some exudates e.g. gum arabic, gum mastic unexposed to a special processing are also considered as herbal substances. The herbal substances are precisely defined with an applicable part of the plant in question and a botanical name in accordance with the binominal system i.e. genus, species, subspecies and author;

“markers” – components or its groups of the herbal pharmaceutical raw materials (herbal substances) or those of a herbal medicinal product with the defined chemical contents that may be interesting for quality control purposes irrespective whether these may possess therapeutic activity or not. The markers are used to estimate an amount of the herbal substance inside a finished medicinal product if the marker has been already exposed to an assay of the herbal substance.

Two categories of markers are defined:

active markers – components or its groups that usually contribute to a therapeutic activity,

analytical markers – components or its groups that are exclusively used for analytic purposes;

“a genuine (native) herbal preparation” – a product based on herbal substance without any excipients even let alone such a product is unavailable for manufacturing reasons. Similarly, both soft and liquid products based on herbal substance may contain a certain number of the solvent (extraction solvent);

“a ratio of herbal substance to a genuine herbal preparation; (DER genuine)” – a proportion between an amount of the herbal substance and an amount of the target genuine preparation. A number expressed as an actual range and specified before a double point stands for a relative amount of the herbal raw materials whereas a number specified after a double point – a relative amount of the yielded/target genuine herbal preparation;

“herbal pharmaceutical substances”, “a herbal preparation” – substances (products) finished after a herbal substance processing by means of such methods as extraction, distilling, pressing, fractionation, purification, concentration and fermentation. These substances (preparations) include comminuted or powder-like pharmaceutical herbal raw materials, tinctures, extracts, etheroleum, succus and processed exudates;

“a solvent” – an inorganic/organic liquid used in solution/suspension preparation in a manufacturing of the herbal substances or of a herbal medicinal product;

“a specification” – a list of tests, references to the analytic and biological methods as well as the relevant acceptance criteria (acceptable limits) representing numerical limits, ranges as well as the other criteria applicable for the described tests. A specification establishes a totality of criteria that the herbal pharmaceutical raw materials (a herbal substance) or a herbal medicinal product must comply with to be considered eligible for its intended indication. When we say “compliance with the specifications”, we mean that the test findings of the herbal pharmaceutical raw materials (a herbal substance) or of a herbal medicinal product pursuant to the analytic methods described in the specifications satisfy the established acceptance criteria. The specifications are mandatory quality standards that are introduced and justified by the manufacturer and approved by the qualified agency as a regulatory submission prerequisite;

“a standardisation” – a method of conditioning a herbal substance to achieve clearly defined contents of either one component or a group of components with a known therapeutic activity by means of adding up excipients or blending multiple lots of herbal substances e.g. standardised extracts;

“extraction solvents” – solvents used in extraction process.

IV. Quality Attributes and Quantitative Characteristics of the Active Ingredient(s) of the Herbal Medicinal Products

7. When drafting specifications it is necessary to pay attention to the following types that all of the herbal substances should be segregated into depending on the manufacturing method:

standardised – those conditioned to contain the established contents of the components with a known therapeutic activity within the permissible limits. A standardisation is achieved by means of adding up excipients into a herbal substance or by means of blending multiple lots of the herbal substances;

quantified (numerical) – those conditioned to achieve a certain range of contents of the components (active markers). Adjustments are achieved exclusively by blending different lots of herbal substances;

others – herbal substances where neither the components with a known therapeutic activity, nor the active markers have been defined.

8. Should any excipients be used in the active substances manufacturing e.g. for manufacturing reasons or for a herbal substance standardisation (conditioning), then it will be necessary to indicate the name and quantity of such excipients.

9. Should either the Pharmacopeia of the Eurasian Economic Union (hereinafter referred to as the Union) or the Pharmacopeias of the Union member-countries contain provisions about the herbal substances, then its name must be indicated both in Russian and Latin. If required, the name of the herbal substance must include both genus and species name. Should the Pharmacopeia of the Union or the Pharmacopeias of the Union member-

countries be void of the monographs about the herbal substances, then its name must be indicated in Latin.

1. A One-Piece Herbal Raw Material, Milled Or Powder-like Pharmaceutical Substances

10. A one-piece herbal raw material is required to indicate that the raw material is one piece. For a milled or powder-like herbal pharmaceutical substance it is necessary to indicate its degree of milling. Also, it is required to indicate the following depending on the chosen method of assay:

а) in case of standardisation. An amount of the herbal pharmaceutical substance should be presented as a range that complies with an established number of components of a known therapeutic activity.

For Example

Active Ingredient Name	Amount
Sennae folium	415-500 mg which complies with 12,5 mg hydroxiantracenic glycosides expressed as sennoside B

б) in case of quantification. An amount of a herbal pharmaceutical substance should be presented as an individual exact value whereas a number of markers should be indicated as a range.

For Example

Active Ingredient Name	Amount
Salicis cortex (willow bark)	4 gr which complies with 40-48 mg of the total of phenolic glycosides expressed as salicin

в) in all the other cases. An amount of a herbal pharmaceutical substance should be presented as an exact value.

For Example

Active Ingredient Name	Amount
Althaeae officinalis radix (therapeutic althea root)	50 gr

2. Herbal Pharmaceutical Substances Retrieved By Means of the Herbal Raw Materials Extraction

11. The herbal pharmaceutical substances retrieved by means of a herbal raw materials extraction are required to indicate a physical form of an extract, type and concentration of the solvent. In addition, the following should be indicated:

a) for standardised extracts: an equivalent amount of the herbal raw materials x-y (*) or a ratio (a-b):1 (*) between the herbal raw materials and the genuine product based on the herbal raw materials. However, an amount of the genuine product may be indicated as a range complying with the relevant defined number of the components with a known therapeutic activity.

For Example.

Active Ingredient Name	Amount
Sennae folium (Senna Leaves) Dry Extract (Extraction Solvent – ethyl alcohol 60% (by volume/ by volume)) ((a-b):1)	50-65 mg which complies with the 12,5 mg of the hydroxiantracenic glycosides expressed as sennoside B

Or

Active Ingredient Name	Amount
Sennae folium (Senna Leaves) Dry Extract (Extraction Solvent – ethyl alcohol 60% (by volume/ by volume))	50-65 mg which complies with the 12,5 mg of the hydroxiantracenic glycosides expressed as sennoside B

(equivalent (x-y) Senna Leaves)

б) for the quantified (indicated) extracts: an equivalent amount of the herbal raw materials x-y (*) or a ratio (a-b):1 (*) between the herbal raw materials and the genuine product based on it. Therefore, an amount of the genuine product should be indicated with an exact value whereas the contents of the quantified herbal raw materials may be presented as a range.

For Example

Active Ingredient Name	Amount
Ginkgo biloba folia (maidenhair tree leaves) Dry Extract (Extraction Solvent – acetone 60% (by volume/by volume)) ((a-b):1)	60 mg which complies with 13,2-16,2 mg flavonoids expressed as the flavonoid glycosides; 1,68-2,04 mg of ginkgolides A, B and C and 1,56-1,92 mg of bilobalide.

Or

Active Ingredient Name	Amount
Ginkgo biloba folia (maidenhair tree leaves) Dry Extract (Extraction Solvent – acetone 60% (by volume/by volume)) (equivalent (x-y) maidenhair tree leaves)	60 mg which complies with 13,2-16,2 mg flavonoids expressed as the flavonoid glycosides; 1,68-2,04 mg of ginkgolides A, B and C and 1,56-1,92 mg of bilobalide.

в) for the other extracts: an equivalent amount of the herbal substances x-y (*) or a ratio (a-b):1 (*) between the herbal substances and the genuine product based on it. However, an amount of the genuine product must be presented with an exact value.

For Example

Active Ingredient Name	Amount
Althaeae officinalis radix (therapeutic althea root)	

Dry Extract (Extraction Solvent – ethyl alcohol 60% (by volume/by volume)) ((a-b):1) Or	125 mg

Active Ingredient Name	Amount
Althaeae officinalis radix (therapeutic althea root)	
Dry Extract (Extraction Solvent – ethyl alcohol 60 % (by volume/by volume)) (equivalent to the (x-y) therapeutic althea root)	125 mg

12. It is required to describe the contents of each extraction solvent or those of its blend as well as its physical form. Should any other substance be added up to achieve the right condition of its constituent components with a known therapeutic activity to comply with the established values or because of any other reason throughout a manufacturing process of a herbal pharmaceutical substance, then it should be specified as “a different substance/ingredient” whereas the genuine extract - as “an active ingredient”.

13. Similarly, should a conditioning of the constituent components of a known therapeutic activity in compliance with the established values or because of any other reason, require different lots of the same extract to be used then the final blend must be considered as a genuine extract and must be labelled as “an active ingredient” in the contents. Also, the regulatory dossier submission must include full data on the manufacturing process and quality control.

V. Description of the Herbal Medicinal Product Manufacturing Process

14. This Chapter understands a manufacturing process as a preparation of a herbal medicine based on herbal raw materials and/or herbal pharmaceutical substances (preparations from the herbal raw materials). So far as the herbal medicines following an abridged dossier submission (traditional herbal medicinal products) are concerned, its manufacturing process is a preparation of a herbal medicine from the herbal raw materials and/or herbal pharmaceutical substances and/or vitamins and/or minerals.

15. A manufacturing process description should include a detailed data on both the process and the measures to ensure quality control. The manufacturing process data should be adjusted in accordance with the Guidance on the manufacturing of the finished dosage form.

16. Should the raw materials be (a) herbal pharmaceutical substance(s), then a description of a process of its preparation and control must be included not in this chapter but in the chapter “Control Of the Raw Materials”.

17. Data about R&D and process validation should be adjusted in accordance with the Guidance on the Pharmaceutical R&D and the Guidance on the Pharmaceutical Manufacturing Process Validation: the data and information for the regulatory dossier submission endorsed by the Commission.

VI. The Raw Materials’ Quality Control

1. A Quality Control of the Herbal Raw Materials/Herbal Pharmaceutical Substances

18. This chapter must be presented in accordance with the Guidance on Specifications: the tests and the acceptance criteria for the herbal raw materials, herbal pharmaceutical substances and herbal medicinal products following an abridged regulatory dossier submission (traditional herbal medicinal products) endorsed by the Eurasian Economic Commission.

Quality Control of the Herbal Raw Materials

19. It is required to submit a full specification for each type of the herbal substances/raw materials. This requirement is valid whenever an applicant and a herbal substances/raw materials manufacturer are two different entities. Should the raw materials be a herbal pharmaceutical substance e.g. in case of fatty oils/etheroleum that are used as active ingredients in the herbal medicinal products, then unless otherwise justified it will be necessary to submit specifications for the herbal pharmaceutical raw materials. The specification must include a scientific name of the herb based on binomial nomenclature e.g. its genus, species, sub-species and author, chemotype if needed as well as the name of the parts of the herb used.

20. Should the Union Pharmacopeia or that of its member-country be void of an individual compendial monograph for a specific type of the herbal raw materials, then it will be necessary to present a full specification for this particular herbal raw material which if practicable must be compiled identically with the individual compendial monographs for the herbal pharmaceutical raw materials in the Union Pharmacopeia. If at all possible, the specification should include data on its habitat, the herbal raw materials' harvesting time, its vegetation stage, pesticides exposure at vegetation, etc., as well as the data on its drying/storage conditions. A full specification must be based on the most recent research data. The herbal pharmaceutical raw materials containing components with a known pharmaceutical activity are required to undergo assay of its contents along with the analytic methods. A content should be indicated as a range to ensure reproducibility of the herbal medicinal quality. In case of the herbal raw materials with no defined components of a known therapeutic activity it will be necessary to arrange an

assay of the markers along with the analytic methods. A choice of markers must be justified.

21. In accordance with a general rule, unless otherwise justified the herbal raw materials are required to undergo tests for microbiological purity (a microbial enumeration test), mycotoxins (aflatoxins, ochratoxin A), residue levels of pesticides, fumigants, toxic elements, potential contaminants, foreign substances, etc. An ethylene oxide utilization to decontaminate herbal raw materials is forbidden. A radionuclides content test is however mandatory. It is required to present specifications and descriptions of the applied analytic methods with the specified acceptance criteria. Analytic methods not described in the Union Pharmacopeia must be validated in accordance with the analytic methods validation guidance unless otherwise justified.

22. To be able to perform comparability studies e.g. macroexamination, chromatography, etc., it is required to keep reference samples of the herbal raw materials.

Quality Control of the Herbal Pharmaceutical Substances

23. If a herbal medicinal product is manufactured based on a herbal pharmaceutical substance, then alongside with a full specification for the herbal raw materials it will be necessary to provide both a description and validation of a manufacturing process of a herbal pharmaceutical substance. This rule is applicable if the applicant and the manufacturer of the herbal pharmaceutical substances are two different entities. This data may be presented as part of the regulatory dossier submission or in the API Master File format (Annex No 10 “An Active Pharmaceutical Ingredient Master File Operating Procedure” in the Guidelines).

24. Should an individual monograph for a herbal pharmaceutical substance be included into the European Pharmacopeia, then an applicant may present a CEP (Certificate of European Pharmacopeia) issued by the EDQM if available.

25. For every herbal pharmaceutical substance a full specification is required which must be compiled based on the most recent scientific knowledge and must include detailed attributes of the product in question and data about its identification/purity tests. It is required to use relevant chromatographic methods. If such a need is conditioned by the test results of the herbal raw materials it will be required to perform tests for microbiological purity (a microbial enumeration test), mycotoxins (aflatoxins, ochratoxin A), residue levels of pesticides, fumigants, toxic elements and solvents if applicable. A radionuclides content test is however mandatory. In addition, it will be necessary to perform assay of the components of a known therapeutic activity or markers. A standardised product shall require contents of the components of a known therapeutic activity to be indicated with a least possible deviation of both the upper and the lower limits.

26. A content of the active markers used for the quantified extracts must be indicated as a set range.

27. In case of the extracts where neither the components of a known therapeutic activity nor the active markers have been determined, a minimum/maximum content of an analytic marker must be specified in relation to the validated analytic range as a basis for analytic suitability as part of the quality control of the batch release procedure. It is required to provide a detailed description of the analytic methods. If the herbal pharmaceutical substances with the components of a known therapeutic activity are standardised i.e. conditioned enough to achieve certain levels of

the constituent components of a known therapeutic activity, then a method of standardisation should be specified. If a standardisation is achieved by means of adding up a different substance, then its amount should be indicated as an acceptable range.

2. A Quality Control of Vitamins and Minerals

28. Both the vitamins and minerals that may be additionally introduced into the contents of the herbal medicinal products with an abridged regulatory dossier submission, there must be a specification in place that has been compiled based on the Specifications Guidance: the tests and acceptance criteria for the herbal pharmaceutical raw materials, herbal pharmaceutical substances and herbal medicinal products, herbal medicines following an abridged regulatory dossier submission (traditional herbal medicinal products).

3. A Quality Control of the Excipients

29. The excipients also including those added up during a process of manufacturing of the herbal pharmaceutical substances should be described in accordance with the requirements of Module Three specified in Chapter Three of Part One in Annex No 1 to the Guidelines, also including a need for compliance with the pharmacopeial monographs of the Union Pharmacopeia or those of its member-countries. So far as the new excipients are concerned, it is necessary to present a detailed data as is required for an active pharmaceutical substance (Chapter 3.2.S of Annex No 1 to the Guidelines).

VII. Herbal Medicinal Products' In-process Controls During Manufacturing

30. It is necessary to submit a detailed data on all the controls with well described analytic methods and acceptable limits for each in-process stage especially if these controls are impossible to perform for the finished herbal medicinal product.

VIII. Controls of the Herbal Medicinal Products

31. This chapter must be presented in accordance with the Specifications Guidance: both the tests and acceptance criteria for the herbal pharmaceutical raw materials, herbal pharmaceutical substances and herbal medicinal products, herbal medicines following an abridged regulatory dossier submission (traditional herbal medicinal products).

32. Analytic methods must be validated in accordance with the Analytic Methods Validation Guidance.

33. The controls of a herbal medicinal product must ensure an opportunity to determine the quality attributes and assay performance of the active ingredient(s). It is necessary to present a specification which may allow utilization of the markers unless the components of a known therapeutic activity have been identified in the contents of a herbal medicine. The components of a known therapeutic activity inherent into the contents of a herbal pharmaceutical substance must be included into the specification and must be exposed to an assay. The herbal medicines with an abridged regulatory dossier submission (traditional herbal medicines) that contain vitamins and/or minerals shall require an inclusion of the vitamins and/or minerals into the specification and this vitamins/minerals content should be indicated.

34. Should a herbal medicinal product contain a combination of several types of the herbal pharmaceutical substances and if there is no opportunity to run each of the API's through an assay, it is allowed to perform a total assay count of multiple active ingredients. However, a need for this assay must be justified.

35. Unless otherwise justified, then a confirmation of the microbiological purity (a microbial enumeration test) should follow the criteria described in the Union Pharmacopeia. A testing frequency needs to be justified.

IX. Stability Studies

36. This chapter must be presented in accordance with the requirements applicable to the stability studies of the medicines from the herbal pharmaceutical raw materials approved by the Commission.

37. Because a herbal pharmaceutical substance is generally regarded as an active ingredient, then a simple identification of the stability of the components of a known therapeutic activity is insufficient. If at all possible, it is required to also prove stability of the other ingredients inherent to the herbal pharmaceutical substance by means of the relevant characterizing chromatograms i.e. fingerprinting analysis. It is also necessary to prove that a relative content shall remain comparable to a primary characterizing chromatogram.

38. Should a herbal medicinal product contain a combination of several types of the herbal pharmaceutical substances when it is impossible to identify stability of each active ingredient, then stability of the medicinal product should be determined by means of the relevant characterizing chromatograms, the relevant methods of the total assay count, as well as the

physical, appearance tests and the other relevant trials. Test suitability must be justified by the applicant.

39. Unless otherwise justified, for the medicinal products that contain a herbal pharmaceutical substance with the components of a known therapeutic activity, a deviation in the content of these components throughout an intended shelf life must not exceed ±5% from a declared assay value. For the herbal medicines that contain a herbal pharmaceutical substance with unidentified components of a known therapeutic activity, it is assumed acceptable to allow a deviation of the marker's content throughout an intended shelf life by ±10% from the primary value unless justified otherwise.

40. In case of the herbal medicines with an abridged regulatory dossier submission (traditional herbal medicinal products) that contain vitamins and/or minerals, stability of vitamins and/or minerals should be proven.

* The values «a» and «b» or «x» and «y» must be justified by the applicant.