Pursuant to Article 24, paragraph 7 of the Law on Medicines („Official Gazette of Montenegro“ No 56/11 and 6/13), the Ministry of Health hereby issues the

# RULEBOOK
# ON MORE DETAILED CONDITIONS AND MANNER OF ENTERING A MEDICINE INTO THE REGISTER OF TRADITIONAL HERBAL MEDICINES

(„Official Gazette of Montenegro” No 04/15 from 28 January 2015)

## I GENERAL PROVISIONS

### Article 1

Traditional herbal medicines shall be entered into the Register of traditional herbal medicines (hereinafter: Register) under conditions defined by this Rulebook.

### Article 2

The terms from this Rulebook used for natural persons in masculine gender shall include the same terms in feminine gender.

### Article 3

The terms used in this Rulebook shall have the following meaning:

1) Herbal substance meets the definition of herbal drug in the European Pharmacopoeia. Herbal substances are defined by botanical, scientific name according to the binomial system (genus, species, variety and author)
2) Herbal preparations meet the definition of herbal preparation in the European Pharmacopoeia. Herbal preparations are homogeneous products obtained by by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include extracts, essential oils, expressed juices, processed exudates, as well as herbal substances subjected to treatments for specific purposes (e.g. comminuted or powdered herbal substances for herbal tea or encapsulating)
3) Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products is a list that contains data on indications, strength, posology, route of administration and any other information necessary for the safe use of the herbal substance in traditional herbal medicine;
4) Committee for Herbal Medicinal Products (HPMC) of the European Medicines Agency (EMA) is a committee that prepares the list of herbal substances (hereinafter: the list), preparations and combinations thereof for use in traditional herbal medicines;
5) Community herbal monograph is a monograph brought by the Committee for Herbal Medicinal Products which contains a summary of pharmaceutical, clinical and pharmacological characteristics of the herbal medicine;
6) A corresponding medicine is a medicine having the same active substance(s), same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the traditional herbal medicine that has been entered into the Register.

## II ENTERING INTO THE REGISTER AND REMOVING FROM THE REGISTER

### Article 4

In order to enter a traditional herbal medicine into the Register, an application on an application form containing data listed below shall be submitted:

1) name of a medicine;
2) a pharmaceutical form, route of administration, data on the packaging;
3) data on the composition of traditional herbal medicine (the name and quantity of active substances and the proposal of the traditional indication(s))
4) data on the manufacturer (name, address and manufacturing site);
5) date and signature of the person responsible for the application for entering into the Register.

The application referred to in paragraph 1 of this Article shall be submitted for each pharmaceutical form, strength and packaging of the traditional herbal medicine.

The application referred to in paragraph 1 of this Article may refer to several applications for entering into the Register, in which case all of them must be clearly stated.

The application form for entering into the Register is available on the portal of the Agency for Medicines and Medical Devices (hereinafter: the Agency).

### Article 5

The application referred to in Article 4 of this Rulebook shall be accompanied by the documentation on a traditional herbal medicine, which includes:

1) qualitative and quantitative particulars of all the constituents of the medicine, including the reference to its international non-proprietary name (INN) recommended by the WHO, where an INN for the medicine exists, or a reference to the relevant name for herbal substance must include scientific name of the plant ((genus, species, variety and author) and used plant part, and for herbal preparations also the relation of herbal substance toward preparation and solvent(s) for extraction.
2) description of the manufacturing method
3) therapeutic indications, contra-indications and adverse reactions
4) posology, pharmaceutical form, method and route of administration and expected shelf life.
5) reasons for precautionary measures to be taken for the storage of the medicine, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicine for the environment
6) description of the control methods employed by the manufacturer
7) pharmaceutical (physicochemical, biological or microbiological) tests and detailed expert report on the quality of the medicine and evidence of adequate qualification of the expert
8) proposed summary of product characteristics, without the data specified in the Article 31 paragraph 1 indent 4 of the Law on Medicines, proposed patient information leaflet and mock-up of inner and outer packaging;
9) manufacturing authorization issued by the competent authority in the country of manufacturer and a certificate on Good Manufacturing Practice of the competent authority or a certificate on good manufacturing practice of regulatory authorities of the European Union Member States
10) list of countries which authorized a medicine for placing on the market, or entered it in the Register, or where it is in the process of obtaining appropriate authorization, as well as a list of countries in which the medicine is marketed, as well as data on rejecting the application in a certain country and reasons for such decision

11) bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the European Union. Under medicinal use it is also considered the use of traditional herbal medicine over a period of 30 years even without marketing authorization or in the case of reduced number or quantity of active substances of the medicine during this period;
12) bibliographic review of safety data together with an expert report, and where required by the Agency, upon additional request, data necessary for assessing the safety of the medicine. (e.g. data on genotoxicity)

The applicant for entering into the Register shall, at the request of the Agency, submit samples of medicines needed for laboratory quality control of medicines.

**Article 6**

If a traditional herbal medicine contains a combination of active substances, in addition to the documentation referred to in Article 5 of this Rulebook, the applicant shall submit the data on traditional use of the medicine showing that it is not harmful if used under the prescribed conditions, as well as that its pharmacological effects or efficacy can be expected based on its long-term use and experience, and which relate to a given combination, as well as the data on the individual active substances, if they are not sufficiently known.

**Article 7**

If the application for entering into the Register refer to the herbal substance, preparation or a combination thereof which are on the list, the applicant is not required to provide information under Article 5, paragraph 1, indents 10, 11 and 12 of this Rulebook.

If the herbal substance, preparation or a combination thereof are no longer on the list, a Decision on entering into the Register issued in accordance with paragraph 1 of this Article shall cease to be valid if the person at whose request traditional herbal medicine was entered into the Register (hereinafter: holder of Registration), within three months does not submit all data and documents in accordance with Article 5, paragraph 1, indents 10, 11 and 12 of this Rulebook.

**Article 8**

Documentation on the medicine referred to in Article 5 of this Rulebook shall be submitted in the form of the Common Technical Document (CTD dossier), with specific requirements for traditional herbal medicines, in accordance with the regulation that determines conditions for issuance of marketing authorization for a medicine.

The specific requirements from paragraph 1 of this Article shall apply to:

1) requirements for herbal substance and herbal preparation;
2) requirements for traditional herbal medicine

Requirements for herbal substance and herbal preparation relate to:

- data related to nomenclature of the herbal substance: the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the description of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code;
- data related to nomenclature of the herbal preparation: the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the description of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code;

- data related to the structure for herbal substance and herbal preparation (where applicable): the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry) as well as other constituents
- data on the manufacturer of the herbal substance: the name, address, and responsibility of each supplier, including contractors, and each site involved in production, i.e. collection and testing of the herbal substance;
- data on the manufacturer of the herbal preparation: the name, address, and responsibility of each manufacturer, including contractors, and each site involved in production, i.e. collection and testing of the herbal preparation, GMP certificate(s) for manufacturing site(s)
- data on the manufacturing process and process controls for the herbal substance: manner of plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions and batch volume
- data on the manufacturing process and process controls for the herbal preparation: manner of manufacturing process with diagram of the production flow, including data on the solvents and reagents, purification stages, standardization, batch volume
- brief summary describing the development of the herbal substance and herbal preparation, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substances and herbal preparations where applicable used in supporting bibliographic data and the herbal substances and herbal preparations, where applicable, contained in the traditional herbal medicine product applied for entering into the Register shall be discussed, where appropriate
- elucidation of the structure and other characteristics of the herbal substance including information on the botanical, macroscopical, microscopical, phyto-chemical characterisation, and biological activity, where appropriate
- elucidation of the structure and other characteristics of the herbal preparation, information on the phyto- and physicochemical characterisation, and biological activity
- specifications for the herbal substance and herbal preparations
- data on the analytical procedures used for testing the herbal substance and herbal preparation
- data on the validation of analytical procedures used for testing the herbal substance and herbal preparation
- data on batches and results of batch analyses for the herbal substance and herbal preparation including those for pharmacopoeial substances;
- justification for the specifications of the herbal substance and herbal preparations
- data on the reference standards or reference materials used for testing of the herbal substance and herbal preparation
- where the herbal substance or the herbal preparation is the subject of a monograph European Pharmacopoeia, the applicant can submit certificate of suitability granted by the European Directorate for the Quality of Medicines.

Requirements for traditional herbal medicine refer to a brief summary describing the development of the herbal medicine, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the products used in supporting bibliographic data and the herbal medicine applied for entering into the Register shall be discussed, where appropriate.

**Article 9**

Entering into the Register is done for a period of validity of marketing authorization for a medicine.

**Article 10**

The Agency may reject the application for entering into the Register, if, in addition to conditions prescribed by the Law, conditions from Articles 5 and 6 of this Rulebook are not fulfilled.

**Article 11**

Holder of Registration may submit an application for amendment to the registration. When herbal substance, preparation or a combination thereof are added to the list, i.e. the adoption of the monograph of the European Union, the holder of Registration containing mentioned substances shall align the data on the medicine (summary of the product characteristics, patient information leaflet, labeling) with the mentioned documents and shall submit the application for the amendment to the registration.

**Article 12**

The holder of Registration shall report to the Agency each amendment to the documentation based on which the traditional herbal medicine was entered in the Register, as well as the causal change in the summary of product characteristics and patient information leaflet.

Along with the application for amendment to the registration referred to in the Article 11 of this Rulebook, the holder of Registration, in addition to the data referred to in Article 4 of this Rulebook, shall submit data on the number and the date of first entry in the Register and the latest renewal (if applicable), with documentation relating to the amendment.

**Article 13**

After the expiry of the period for which entering was made, holder of Registration shall apply for the renewal of the entering in the Register.

Along with the application for amendment to the registration, the holder of Registration, in addition to the data referred to in Article 4 of this Rulebook, shall submit data on the number and the date of first entry in the Register and latest renewal (if applicable), with documentation relating to the renewal.

An applicant for renewal of registration shall, at the request of the Agency, submit samples of medicines needed for laboratory quality control of a medicine.

**Article 14**

The documentation referred to in Article 13 paragraph 2 of this Rulebook, shall contain:

1) updated administrative data from Article 5 of this Rulebook;
2) chronological list of approved and submitted amendments during the validity period of entering in the Register;
3) review the data on the safety of traditional herbal medicine in the past five years.

**Article 15**

Removing traditional herbal medicine from the Register is done at the request of the holder of Registration, or in case that the Agency determines that:

1) validity period of entry in the Register expired, and no application for renewal was submitted;
2) medicine does not meet the quality and safety standards in the prescribed conditions of use;
3) marketed medicine does not comply with the terms of the Decision on entering in the Register;

4) Decision on entering in the Register was issued on the basis of incomplete and inaccurate data, or, if the data is not amended in accordance with the Law and the regulations adopted for its implementation;
5) holder of Registration no longer meets the prescribed requirements;
6) medicine is placed onto the market contrary to the provisions of the Law and regulations adopted for its implementation;

**Article 16**

Labeling of traditional herbal medicines is done in accordance with special regulations.

**III FINAL PROVISION**

**Article 17**

This Rulebook shall enter into force on the eighth day of its publication in the "Official Gazette of Montenegro".

Number: 011-258/2014
Podgorica, 20 January 2015

Acting Minister of Health
Dr Suad Numanović, m.p.
Minister for Human and Minority Rights