

Based on Article 105 paragraph 12 of the Law on medicines („Official gazette of Montenegro” No 14/26),

The Management Board of the Institute with the consent of the Ministry of Health adopted

RULEBOOK ON CONDITIONS FOR MANUFACTURING OF ACTIVE SUPSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE

I GENERAL PROVISIONS

Article 1

This rulebook prescribes the detailed conditions for manufacturing, the content of applications for registration, as well as amendments and/or supplements to the registration of manufacturers in the Register of manufacturers, importers and/or distributors of active substances (hereinafter: the Register) and principles and guidelines of good manufacturing practice for active substances for medicinal products.

This rulebook also applies for active substances intended only for export.

Article 2

Terms used in this Rulebook for natural persons in masculine gender include the same terms in feminine gender.

Article 3

Terms used in this rulebook shall have the following meaning:

- 1) **manufacturing of active substances** means any total or partial operation of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control or release of active substances, and the related controls;
- 2) **active substance starting material** means any substance from which an active substance is manufactured or extracted;
- 3) **active substance intermediate** means a substance which is obtained during the production of an active substance and which is intended for further processing;
- 4) **raw material** means any substance, reagent or solvent which is intended for use in the production of an active substance and from which the active substance is not directly manufactured or extracted.

II CONDITIONS FOR MANUFACTURE

Quality management

Article 4

Manufacturers of active substances, shall establish, document and implement an effective pharmaceutical quality system, involving the active participation of the senior management and the personnel of the different departments.

The quality system for active substances shall ensure that the active substances meet the specifications for their quality and purity established in accordance with article 13 paragraph 1 of this rulebook.

The quality system for active substance shall incorporate quality risk management.

The manufacturer of active substances shall appoint a quality unit that is independent of the production unit to be responsible for quality assurance and quality control.

The manufacturer of active substances shall conduct regular internal audits and follow-up on the findings.

Personnel

Article 5

The manufacturer of active substance shall ensure an adequate number of personnel having the necessary qualifications acquired through education, training or experience to carry out and supervise the manufacturing of active substances.

Personnel shall practice good sanitation and hygiene in the manufacturing area. Personnel shall not access the manufacturing area if they:

- 1) suffer from an infectious disease or have open lesions or other dermatological conditions on the exposed surface of the body that could negatively affect the quality and purity of the active substance;
- 2) wear clothing which is visibly dirty, or does not protect the active substance from potential contamination coming from personnel, or does not protect personnel from exposure to active substances potentially harmful to human health;
- 3) at the moment of entering the manufacturing area, are performing activities that could contaminate or otherwise compromise the quality of the active substance.

Buildings and facilities

Article 6

Buildings and facilities used in the manufacturing of active substances shall be located, designed and constructed to suit the intended operations and to facilitate cleaning and maintenance having regard to the type and stage of manufacturing which the buildings and facilities are used for.

Facilities and the flow of material and personnel through the facilities referred to in paragraph 1 of this article shall be designed to ensure that different substances and materials are kept separate and do not contaminate each other.

Buildings referred to in paragraph 1 of this article shall be properly maintained and repaired and kept in a clean condition.

Highly sensitising active substances shall be produced in separate production areas.

When carrying out production operations, the manufacturer shall assess the need for separate production areas for other active substances with the potential to be harmful to human health because of their potency or their infective or toxic nature. The assessment shall evaluate the risk to human health posed by those active substances by taking account of the active substance potency, toxicity, infectivity and the risk minimisation procedures in place. The

assessment shall be documented in writing. Where the assessment shows a risk of harm to human health, the active substance shall be produced in separate production areas.

Equipment

Article 7

Equipment used in the manufacturing of active substances shall be appropriately designed, sized and located for its intended use, cleaning, maintenance and, where appropriate, sanitisation.

Equipment shall be constructed and operated so that surfaces that come into contact with raw materials, active substance starting materials, active substance intermediates or active substances do not alter the quality of the raw materials, the active substance starting materials, the active substance intermediates or the active substances to the extent that they no longer comply with the specifications established in accordance with article 13 paragraph 1 of this rulebook.

The manufacturer shall establish written procedures for the cleaning of equipment and the subsequent verification of its suitability for use in the manufacturing process.

Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of the active substance shall be calibrated in accordance with written procedures and an established schedule.

Documentation and records

Article 8

The manufacturer of active substance shall establish and maintain a documentation system and written procedures covering the manufacturing process

All documents in relation to the manufacturing process of active substance shall be prepared, reviewed, approved and distributed in accordance with written procedures.

The manufacturer of active substance shall maintain records of at least the following elements in relation to the manufacturing process:

- 1) equipment cleaning and use;
- 2) origins of raw materials, active substance starting materials and active substance intermediates;
- 3) controls in relation to raw materials, active substance starting materials and active substance intermediates;
- 4) use of raw materials, active substance starting materials and active substance intermediates;
- 5) labelling of the active substances and of the packaging materials;
- 6) master production instructions;
- 7) batch production and control;
- 8) laboratory controls.

The issuance, revision, replacement and withdrawal of documents related to the manufacturing process shall be controlled, and records of their revision, replacement and withdrawal shall be kept.

All quality related activities carried out during the manufacturing process shall be recorded at the time they are performed. Any deviation from the written procedures referred to

in paragraphs 1-4 of this article shall be documented and explained. Deviations affecting the quality of the active substance or preventing the active substance from meeting the specifications referred to in article 13 paragraph 1 shall be investigated, and the investigation and its conclusions shall be documented.

After carrying out production and control operations, the manufacturer shall retain all production and control records for at least one year after the expiry date of the batch. For an active substance with retest dates, the manufacturer shall retain records for at least three years after the complete batch has been placed on the market.

Material management

Article 9

The manufacturer of active substance shall have written procedures in place for ensuring the quality of incoming material covering the following elements:

- 1) receipt;
- 2) identification;
- 3) quarantine;
- 4) storage;
- 5) handling;
- 6) sampling;
- 7) testing;
- 8) approving;
- 9) rejection.

The manufacturer of active substance shall have a system in place for evaluating suppliers of critical materials.

Production and in-process control

Article 10

Production operations shall be subject to controls in order to monitor and adjust the production process or verify that the active substance conforms to the specifications of quality and purity pursuant to article 13 paragraph 1 of this rulebook. Production operations which are critical to ensure that the active substance meets the quality specifications referred to in article 13 paragraph 1 of this rulebook shall be carried out under the visual supervision of qualified personnel or subjected to an equivalent control.

Weighing and measuring of raw materials and active substance starting materials shall be accurate and shall be conducted in a manner which does not affect their suitability for use.

Active substance production operations, including any operation after purification of the active substance intermediates or the active substance, shall be conducted in a manner that prevents raw materials, active substance starting materials, active substance intermediates and active substances from being contaminated by other materials.

Packaging and labelling

Article 11

Containers shall provide adequate protection against deterioration or contamination of the active substance from the moment the active substance is packaged to the moment it is used in the manufacturing of medicinal products.

Storage, print and use of labels on the packaging of active substances shall be controlled. Labels shall contain the information necessary to assure the quality of the active substance.

Placing on the market

Article 12

An active substance shall only be placed on the market after it has been released for sale by the quality unit.

Where the active substance is repackaged by a manufacturer in a container which differs from the original container with regard to its volume, or the material it is made of, or its opaqueness to light, he shall conduct stability studies on the active substance and assign an expiration or retest date for it on the basis of those studies.

Laboratory controls and validation

Article 13

The manufacturer of active substance shall establish specifications for the quality and purity of the active substances he manufactures and for the raw materials, active substance starting materials and active substance intermediates used in that process.

Laboratory tests shall be conducted to verify compliance with the specifications referred to in paragraph 1 of this article.

The manufacturer of active substance shall issue certificates of analysis for each batch of active substance upon the request of:

- 1) the Institute;
- 2) manufacturers of active substances supplied directly or indirectly with the active substance for the purpose of further processing, packing, repacking, labelling or relabelling the active substance;
- 3) distributors and brokers of active substances;
- 4) manufacturers of medicinal products supplied directly or indirectly with the active substance.

The manufacturer of active substance shall monitor the stability of the active substance through stability studies. Dates for the expiry or retest of active substances shall be set on the basis of an evaluation of data derived from the stability studies. Appropriately identified samples of the active substance shall be retained in accordance with a sampling plan established on the basis of the shelf-life of the active substance.

The manufacturer of active substance shall set up and implement a validation policy for those processes and procedures that are critical to ensure that the active substance meets the quality and purity specifications established in accordance with paragraph 1 of this article.

Change control

Article 14

The manufacturer shall evaluate the potential impact on the quality of the active substance of any changes to the manufacturing process that may affect the production and control of the active substance before implementing those changes.

Changes to the manufacturing process that negatively affect the quality of the active substance shall not be implemented.

The manufacturer of an active substance shall notify without delay the manufacturers of medicinal products which he supplies with the active substance of any changes to the manufacturing process that may impact the quality of the active substance.

Complaints, returns and recalls

Article 15

Batches of active substances and active substance intermediates failing to conform to the specifications established in accordance with article 13 paragraph 1 of this rulebook shall be rejected, labelled as such and quarantined.

The manufacturer of active substance who reprocesses or reworks rejected batches of an active substance that do not conform to specifications, or recovers raw materials and solvents for re-use in the manufacturing process, shall follow the procedures established in accordance with article 8 paragraphs 1 – 4 of this rulebook and shall perform appropriate controls to ensure that:

- 1) the reprocessed or reworked active substance meets the quality specifications established in accordance with article 13 paragraph 1 of this rulebook;
- 2) the recovered raw materials and solvents are suitable for their intended use in the manufacturing process.

Returned active substances shall be identified as such and quarantined.

The manufacturer shall record and investigate all quality related complaints.

The manufacturer shall establish procedures for the recall of active substances from the market.

In the event of the recalled active substance posing a serious threat to public health, the manufacturer shall inform the Institute and competent authorities without delay.

Contract manufacturing

Article 16

A manufacturing operation or an operation linked thereto which is to be carried out on behalf of the manufacturer of the active substance by another party (hereinafter: the contract manufacturer) shall be the subject of a written contract.

The contract from paragraph 1 of this article shall clearly define the responsibilities of the contract manufacturer with regards to good manufacturing practice.

The manufacturer of the active substance shall control that operations carried out by a contract manufacturer comply with good manufacturing practice.

A manufacturing operation or an operation linked thereto which has been entrusted to a contract manufacturer shall not be subcontracted to a third party without the written consent of the manufacturer of the active substance.

III CONTENT OF THE APPLICATION FOR REGISTRATION OF MANUFACTURER

Article 17

The application for entry into the Register shall be submitted by the manufacturer of the active substance to the Institute in accordance with the Law and this rulebook.

The application referred to in paragraph 1 of this article shall be submitted using the application form published on the official website of the Institute.

Along with the application referred to in paragraph 1 of this Article, the applicant shall submit documentation in accordance with the article 105 paragraph 3 of the Law.

The manufacturer of the active substance shall, along with an application for amendment or supplementation of the entry in the Register, submit a description of the amendment or supplement with justification and the required documentation. In the case of an application for

deletion from the Register, the manufacturer shall provide substantiated reasons for ceasing the activity.

Proof of payment of the prescribed fees shall be submitted along with the applications referred to in paragraphs 1 and 4 of this article.

IV INSPECTION OF COMPLIANCE WITH GMP GUIDELINES

Article 18

Following the entry into the Register, or prior to the expiration of the period for which the GMP certificate was issued, the manufacturer of active substances shall submit an application for the issuance of a GMP certificate in accordance with the Law.

The GMP certificate is issued for various manufacturing activities related to the production of the active substance.

The application referred to in paragraph 1 of this article shall be submitted using the application form published on the official website of the Institute.

Along with the application referred to in paragraph 1 of this Article, the manufacturer shall submit documentation demonstrating compliance with GMP guidelines, in accordance with the request of the Institute.

Proof of payment of the prescribed fees shall be submitted along with the application referred to in paragraph 1 of this article.

Article 19

Within 7 days from the last day of the GMP inspection, inspector of the Institute shall issue Minutes of the GMP Inspection and deliver it to the inspected entity.

In the event that deficiencies are identified during the inspection referred to in paragraph 1 of this article, the applicant shall submit a written response to the inspector of the Institute regarding the identified deficiencies no later than 30 days from the receipt of the Minutes of the GMP Inspection and shall propose corrective and preventive measures along with deadlines for resolving the identified deficiencies.

In cases of incomplete or unacceptable responses, the inspector shall request additional documentation from the inspected entity requiring correction or supplementation of the written response, and shall set a deadline for submission.

During this period, the deadline from paragraph 3, for issuing the GMP certificate is suspended.

Inspector of the Institute shall issue a Report on the Application of Good Manufacturing Practice Guidelines (GMP Inspection Report) based on the Minutes of the GMP Inspection, and in cases of identified deficiencies, also based on the written response of the inspected entity.

Article 20

GMP certificate serves as proof of compliance with GMP guidelines for the manufacturing site of the medicinal product or active substance at the time of inspection, for a period of up to three years from the date the inspection was conducted.

Exceptionally from paragraph 1 of this article, inspector of the Institute may decide to extend or shorten the validity period of the GMP certificate based on a risk assessment.

Article 21

If it is determined during the inspection that the manufacturer no longer performs activities in accordance with the requirements of good manufacturing practice, the Institute may suspend or revoke the GMP certificate, or issue a Statement of Non-Compliance with GMP Guidelines.

V FINAL PROVISION

Article 22

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

No.

PRESIDENT OF THE BOARD OF DIRECTORS

In Podgorica, 2026

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