CInMED
Institut za ljekove
i medicinska sredstva Crne Gore
Institute for Medicines and
Medical Devices of Montenegro

MANNER OF SUBMITTING APPLICATION AND DOCUMENTATION FOR OBTAINING MARKETING AUTHORIZATION FOR MEDICINES FOR HUMAN USE

Application for the issuance of a marketing authorization for a medicinal product for human use shall be submitted to the Institute for Medicines and Medical Devices (hereinafter: CInMED) at a previously scheduled term via telephone: **+382 20 310 280.**

The application for the issuance of a marketing authorization shall be prepared in accordance with the Law on Medicines ("*Official Gazette of Montenegro*" Nos. 80/20, 84/24 and 35/25) and the Rulebook on More Detailed Conditions for the Issuance of a Marketing Authorization („*Official Gazette of Montenegro*" Nos. 21/16 and 55/19).

All documentation, except for the cover letter (which shall be submitted in paper form), must be submitted exclusively in electronic format, in the following file types: Word documents (docx), Excel worksheets (xlsx) and PDF, following the CTD format. Documentation for each module (1–5) shall be submitted in a separate folder, clearly labelled with the module name (e.g., Module 1, Module 2, Module 3, Module 4, Module 5), whereby all documents belonging to a given module must be included strictly within the corresponding folder. Document names must be specified so as to clearly and unambiguously describe the content of the document. The same principle applies when submitting additional documentation. The Representation Agreement may be submitted either in paper and/or electronic form.

Documentation in paper form shall be submitted in A4 file folders, with the following information on:

- Name of the medicine, strength, pharmaceutical form, type and size of package;
- Applicant;
- Manufacturer.

In accordance with the Article 46 of the Law, the Institute, in the procedure of granting a marketing authorization for a medicinal product, does not assess whether there is an infringement of intellectual or industrial property rights. Protection marks of the medicinal product name shall not be indicated in the documents submitted with the application for the marketing authorization.

Application for Marketing Authorization for a medicine shall be accompanied by:

MODULE 1 – Administrative data

1.0. Cover letter for the marketing authorization application shall be submitted using the template available on the CInMED portal.

1.1. Content

1.2. Application form for issuance of marketing authorization, prepared using the template available on the CInMED portal.

- The form itself must not be altered. Sections of the form that are not applicable to the application shall be marked as N/A (Not Applicable) - parts that cannot be filled in due to lack of data must not be deleted;
- The form shall be filled in electronically, signed by the person responsible for obtaining the marketing authorization, with the seal of the applicant or signed with an electronic signature and electronic seal in accordance with the law governing electronic identification and electronic documents (the form shall not be submitted as a scanned copy of an electronically signed document);
- The applicant shall submit a completed application form for each pharmaceutical form, strength, type and pack size of the medicinal product;
- When entering data on the pharmaceutical form, packaging and route of administration, it is necessary to use EDQM standard terms.

As an attachment to the application form, the following documentation shall be submitted in electronic format:

➢ **Documentation for manufacturing site(s) of active substance and a medicinal product**

Flow chart for Montenegro – The chart must indicate the name and address of the manufacturers involved in all stages of active substance manufacturing (including the sites of intermediate production, as well as micronization and sterilization, where applicable) and finished product manufacturing. The data on the names, addresses and roles of the manufacturers must be consistent with the information provided in Module 3. In cases where the flow chart lists only batch release sites for the EU, it is necessary to explicitly indicate whether the same manufacturers are responsible for batch release in Montenegro as well.

For all sites involved in the manufacturing process of active substance and intermediates (including the site of micronization, where applicable), a Qualified Person (QP) declaration confirming compliance with GMP requirements shall be provided, from:

- the manufacturer which uses the active substance as a starting material (if established in the EEA member states), and
- the manufacturer of a medicinal product responsible for batch release.

It is also possible to submit a single QP declaration on behalf of manufacturers of a medicinal product who are required to provide a QP declaration. The QP declaration shall be prepared in accordance with the current version of the EMA guideline: *Guidance for the template for the qualified person's declaration concerning good manufacturing practice (GMP) compliance of active substance manufacture "The QP declaration template*".

For manufacturing sites of sterile active substances, a valid GMP certificate issued by the regulatory authority of an EEA Member State or an EUMRA country, shall also be provided.

* If the quality of the active substance is covered by the CEP certificate (*European Pharmacopoeia Certificate of Suitability*), in addition to being provided under section 3.2.R, a copy of the CEP certificate with the completed *Declaration of Access* section must also be submitted in Module 1, or, where applicable, a *Letter of Access* using the template available on the EDQM website.

**If the documentation on the active substance is submitted in the *Active Substance Master File* (ASMF) format, in addition to being an integral part of section 3.2.S submitted by the local representative of the manufacturer, the ASMF holder is required to provide both the open part (ASMF *applicant's part*; AP) and the closed part (ASMF *restricted part*; RP). The version of the ASMF AP submitted by the ASMF holder must be identical to the version submitted within section 3.2.S of the dossier. Together with the ASMF, a *Letter of Access* and/or a *Submission Letter* shall be provided in accordance with Annex 2 and Annex 3 of the *Guideline on Active Substance Master File Procedure, CHMP/QWP/227/02 Rev 4/ Corr.*

The ASMF AP and RP shall be submitted electronically by the ASMF holder, via the following link: https://secure.cinmed.me//eservis/strani-korisnik.

When submitting the ASMF AP and RP, it is necessary to clearly indicate in the field "short description" the procedure to which the documentation relates (e.g. marketing authorization, variation, submission of responses during clock stop, etc.), as well as the name of the medicinal product and the reference number (if available).

Exceptionally, for medicinal products authorized through the centralized procedure in the European Union, the ASMF RP shall be submitted only upon request of the Institute.

For all sites involved in the manufacturing process of the medicinal product, the following shall be submitted:

- valid evidence of compliance with Good Manufacturing Practice requirements (GMP certificate) issued by the regulatory authority of an EEA member state or an EUMRA country
- Manufacturing Authorization.

➢ **Overview of the marketing authorization status of the medicinal product in other countries**

An overview shall be provided of the countries in which a marketing authorization has been granted, in which the authorization has been withdrawn as well as the countries where the authorization procedure is ongoing. For each country, the approved name of the medicinal product, the authorization number and date, and information on whether the product has been placed on the market shall be specified. If the application for a marketing authorization has been refused in any country, a justification of the reasons for refusal shall be submitted.

- **Copies of the Marketing Authorization(s) (or decision on the renewal of Marketing Authorization) in other countries**

Along with Marketing Authorization (or decision on the renewal of the Marketing Authorization), it is necessary to submit the latest approved texts of the Summary of Product Characteristics (SPC) and the Package Leaflet (PL) in a particular country.

- **Documentation on the applicant**
  - Excerpt from the Central Register of Business Entities (CRPS) in Montenegro
  - Representation agreement (which must include the authorization to act on behalf of the applicant in the territory of Montenegro, the list of products and established liability insurance for potential damages arising from the use of the medicinal product in Montenegro). The original shall be submitted either in paper or electronic form, in accordance with the law governing electronic identification and electronic documents, or as a notarized copy of the agreement.

If the applicant submitted given documentation with one of the previous applications, it is not necessary to submit the same documentation when submitting new applications (as long as given documents are valid), but only to specify with which previous subject/application the documentation in question was submitted.

Responsible persons

Responsible person for obtaining the marketing authorization, variation and renewal of the authorization

- Statement of the responsible person of the applicant/Marketing Authorization Holder (MAH) appointing the responsible person for obtaining the marketing authorization, variation and renewal of the authorization;
- Proof of employment - the applicant/MAH shall submit full-time employment contract with the responsible person, defining the obligations of the appointed person in relation to obtaining, varying, amending and renewing the marketing authorization, in accordance with the applicable regulations;
- Proof of professional qualifications;
- Confirmation from Tax Administration on registered employment insurance;
- Curriculum Vitae (CV).

Responsible person for pharmacovigilance

- Statement of the responsible person of the applicant/Marketing Authorization holder appointing responsible person for pharmacovigilance, including confirmation that the appointed person for pharmacovigilance is available 24 hours a day. The statement must specify 24-hour contact details of the pharmacovigilance responsible person (mobile phone, e-mail);
- Proof of employment - the applicant/MAH shall submit full-time employment contract with the pharmacovigilance responsible person, defining the obligations of the appointed person in relation to pharmacovigilance in accordance with the applicable regulations;
- Proof of residence - copy of ID card or confirmation of residence issued by the competent

authority;
- Proof of appropriate professional qualifications - Article 44 paragraph 5 of the Law on Medicines;
- Confirmation from Tax Administration on registered employment insurance;
- Curriculum Vitae (CV).

If the applicant submitted given documentation with one of the previous applications, it is not necessary to submit the same documentation when submitting new applications (as long as given documents are valid), but only to specify with which previous subject/application the documentation in question was submitted.

1.3. Summary of product characteristics, labeling and package leaflet

Proposals of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) shall be submitted in Montenegrin, using the templates available on the CInMED portal (in Word format, docx). If the abridged application is submitted, the SmPC and PL texts of the original (reference) medicinal product, on the basis of which the draft texts of the SmPC and PL for Montenegro have been prepared, shall also be submitted.

Proposal of the labelling of the outer and immediate packaging of the medicinal product shall be submitted in accordance with the Rulebook on the Contents and Manner of Labelling the Outer and Immediate Packaging of a Medicinal Product and the Contents of the Package leaflet ("*Official Gazette of Montenegro*" Nos. 21/16 and No 67/18) (hereinafter: the Rulebook on labelling).

Proposal of the labelling in Montenegrin shall be submitted using the template available on the CInMED portal (in Word format, docx).

For medicinal products whose outer packaging is labelled in a foreign language, the following shall be submitted:
- mock-up/labelling of the approved foreign packaging;
- draft of the additional label in accordance with Article 25 of the Rulebook on labelling;
- declaration of identity of the documentation approved by the competent authority in the country of origin of the proposed packaging and the documentation submitted to CInMED. The declaration must include confirmation that the documentation, including all variations and amendments, is identical to the documentation approved by the competent authority in the country of origin of the proposed packaging. If there are differences in the documentation, these must be listed and explained;
- declaration of the applicant confirming that the annual consumption of the medicinal product in Montenegro will be below 5,000 packs.

For medicinal products whose outer packaging is labelled in a language in official use in Montenegro, the following shall be submitted:

- mock-up/labelling of the approved packaging;
- draft of the additional label in accordance with Article 26 of the Rulebook on labelling;
- declaration of identity of the documentation approved by the competent authority in the country of origin of the proposed packaging and the documentation submitted to CInMED. The declaration must include confirmation that the documentation, including all variations and amendments, is identical to the documentation approved by the competent authority in the country of origin of the proposed packaging. If there are differences in the documentation, these must be listed and explained.

If an application for a marketing authorization is submitted under the accelerated procedure and the proposed packaging of the medicinal product originates from a country that did not participate in the EU procedure referred to, a declaration of identity must also be submitted, confirming that the documentation approved in the EU procedure is identical to the documentation approved in the country of origin of the packaging. Any differences at the level of the approved documentation must be specified and explained. The declaration must also include a list of variations submitted in the EU procedure and in the country of origin of the proposed packaging, their status (submitted, approved) and information on whether these have been implemented in the dossier submitted in Montenegro.

Results of the readability testing of the Package Leaflet, carried out in cooperation with target patient groups in accordance with the European Commission guideline *"Guideline on the readability of the labelling and package leaflet of medicinal products for human use"* (User test/Readability testing), shall be submitted, or a justification for its omission shall be provided.

1.4. Information on experts

Curricula Vitae (CVs) of the experts who prepared the expert summaries on the pharmaceutical-chemical-biological, pharmacological-toxicological and clinical documentation shall be submitted, together with signed declarations of the experts indicating the date of preparation of the submitted expert summaries.

1.5. Specific conditions for different types of application (explanation for the type of application)

It is necessary to submit explanation and evidence of the type of application in accordance with Annex 2, part II of the Rulebook on More Detailed Conditions for Issuance of Marketing Authorization for a Medicine ("Official Gazette of Montenegro" No 21/16 and 55/19) - Specific Marketing Authorization dossiers and requirements.

1.6. Environmental Risk Assessment, in accordance Rulebook on More Detailed Conditions for Issuance of Marketing Authorization for a Medicine, or justification for the omission of it.

1.7. Information on medicines for the treatment of rare diseases in humans ("*Orphan*" medicines), if applicable.

1.8. Documentation pertaining to pharmacovigilance

- Summary of the EU and local PSMF. The summary of the EU and local PSMF shall contain the information prescribed by the Law on Medicines, Article 46, paragraph 1, point 12;
- The most recent PSUR/PBRER for medicinal products for which submission is required according to the EURD list;
- If the submission frequency of the PSUR/PBRER is not determined by the EURD list, it is necessary to provide a statement with a proposal of frequency of submission of PSUR/PBRER after obtaining marketing authorization;
- The most recent RMP. For medicinal products without an RMP, the marketing authorization holder shall provide a statement confirming that an RMP has not been submitted and explaining the reasons for its non-submission;
- A statement on additional risk minimization measures, including a proposal for their implementation, where additional risk minimisation measures are required.

1.9. Information on clinical trials, if applicable

- Statement confirming that clinical trials conducted outside of European Union Member States meet ethical requirements in accordance with regulations on clinical trials in the European Union.

The applicant shall also submit a risk assessment report on the potential presence of nitrosamine impurities in the active substance and the finished medicinal product, in accordance with EMA decision EMA/341963/2020 of 9 July 2020 and guideline EMA/409815/2020. The corresponding report and documentation shall also be provided in Module 3.

Module 2 – Expert summaries on quality, safety and efficacy

2.1. Table of Contents
2.2. Introduction
2.3. Quality Overall Summary
2.4. Nonclinical Overview
2.5. Clinical Overview
2.6. Nonclinical Written and Tabulated Summaries
2.7. Clinical Summary

Module 3 - Quality

Module 4 - Nonclinical Study Reports

Module 5 - Clinical Study Reports

The applicant shall submit a statement undertaking to provide the standards and samples necessary for quality control, upon request of the Institute, no later than within 30 days.

For applications for a marketing authorization under the accelerated procedure, in accordance with Article 62 of the Law on Medicines, the following documentation shall also be submitted:

- identical documentation (a consolidated file covering Modules 2 - 5) that has been approved in the centralized procedure (CP), decentralized procedure (DC) or mutual recognition procedure (MRP);
- a statement by the applicant confirming that the documentation submitted for the marketing authorization application in Montenegro is identical to the documentation on the basis of which the Assessment Report was prepared and issued, including all variations approved up to the date of submission of the application, and that the submitted documentation is valid in the Member States of the European Union. In cases where there are differences compared to the documentation approved in CP, DC or MRP, these must be clearly stated and explained;
- a list of variations submitted and approved in the CP, DC or MRP up to the date of submission of the application to CInMED, including information on the status of each variation in the procedure, as well as whether they have been implemented in the dossier submitted to CInMED. For variations that have been approved and implemented, the relevant approvals from the CP, MRP or DC procedure shall be submitted;
- the Assessment Report (Final Assessment Report) issued by the EMA or the Reference Member State in the DC and MRP procedures, as well as the Quality, Non-clinical and Clinical Assessment of the responses to the outstanding questions raised by the RMS and CMSs, as well as the preliminary reports from all stages of the MRP or DC procedure;
- a statement by the applicant undertaking to notify the Institute without delay in the event of permanent or temporary withdrawal of the marketing authorization in the European Union, as well as of any urgent safety measures.

Note: If the application for a marketing authorization in Montenegro is submitted before the completion of the CP, DC or MRP procedure, the basic requirement of identity between the submitted documentation and the documentation approved in the CP, DC or MRP procedure is not fulfilled, and the application cannot be considered under the accelerated procedure in accordance with Article 62 of the Law on Medicines.