Best share practice

FOR HIGHER QUALITY PREPARATION OF REGISTRATION DOCUMENTATION (MODULE 1)

In order to ensure adequate availability of high-quality, safe and effective medicinal products to the citizens of Bosnia and Herzegovina, the Agency is publishing the *Best share practice* for higher quality preparation of registration documentation (Module 1) under assessment in the procedures for granting/renewing a marketing authorisation for a medicinal product.

The documentation prepared in accordance with the requirements of the national legal framework and European standards for quality, efficiency and safety enables its faster assessment and a faster completion of the procedure, and thus the availability of the, by this Agency, checked and approved medicinal product.

Unfortunately, we, on a daily basis, encounter the documentation submitted together with the application, which has many deficiencies or insufficient documents.

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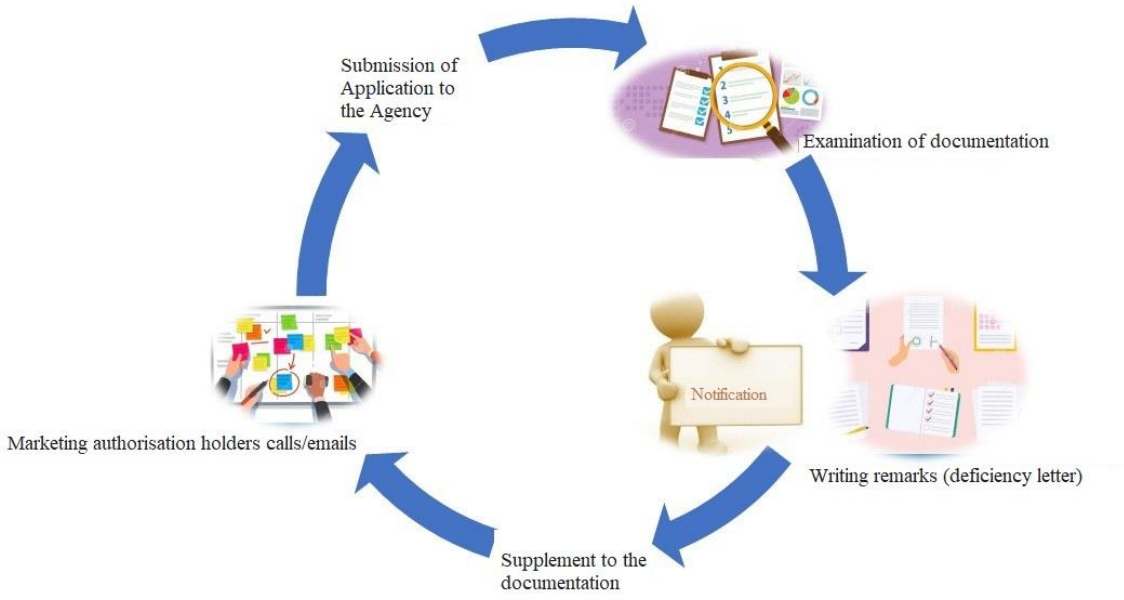

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FOR HIGHER QUALITY PREPARATION OF REGISTRATION DOCUMENTATION (MODULE 1)

In the following text, we are providing you with an overview of frequent deficiencies that require a halt in the procedure at the formal completeness assessment phase (validation and regulatory assessment) and submission of new documents. At the same time, along with the indicated deficiencies, we are providing you with instructions for overcoming them.

We hope that through joint efforts we will reach the successful realisation of the goal of protecting the public health of the population.

Sincerely,

ALMBIH

10. Cover Letter

Basic information on the medicinal product should be provided. If the proposer submits an application in accordance with the *Fast Track* procedure, which is defined in Articles 32. and 33. of the Ordinance on the Procedure and Manner for Granting a Marketing Authorisation for a Medicinal Product ("Official Gazette of BiH", no. 75/11) hereinafter: Ordinance, it should be noted in the Cover Letter.

12. An application for granting a marketing authorisation for a medicinal product

All information specified in the application must be derived from the documentation accompanying the application:

- There are frequent errors in marking the type of application. The type of application must be chosen in accordance with the explanation (point 1.5.1 or 1.5.2 of *NeeS*) and with the enclosed documentation;
- It is necessary to indicate the countries of the European Union (hereinafter: EU) in which the medicinal product has been authorised.
- It is necessary to state the name of the manufacturer correctly, in accordance with the Decision of the Ministry of Foreign Trade and Economic Relations.
- Manufacturers must be indicated in accordance with the following:
  - enclosed *Flowchart*,
  - information on manufacturers presented in Module 3 and
  - enclosed valid *GMP* certificates and manufacturing authorisations.

It is not necessary to specify the manufacturers of intermediates.

- Information related to the period of use of the medicinal product and the conditions of storage of the medicinal product must be in accordance with the information on stability specified in Module 3.
- Information related to the medicinal product packaging size and the composition of the primary packaging of the finished medicinal product must be in accordance with the information specified in section 6.5 of the *SmPC* proposal and in part 3.2.p.7 of Module 3.

- Information on the name and address of the legal entity/representative, which are specified on the application, must be consistent with the information specified in the Extract from the court register and the information specified in the Decision of the Ministry of Foreign Trade and Economic Relations.

111. Evidence of entry of the proposer/representative in the court register, the document must not be older than 6 months

- It is necessary to submit a valid extract from the court register, not older than 6 months on the date on which the application was submitted.

112. Valid Decision of the Ministry of Foreign Trade and Economic Relations certifying the Contract on Representation between the proposer/representative and the manufacturer

- The Decision must be valid (in case the duration of the Decision is limited),
- The Decision should include the representative's current address,
- The Decision should include the current name and address of the manufacturer,
- For the manufacturer, it is necessary to enclose a valid manufacturing authorisation.

113. Valid Contract on Representation in one of the languages that are in official use in BiH with a manufacturing authorisation of the manufacturer with whom the Contract on Representation is concluded

A tripartite contract is not acceptable.

The Contract on Representation is valid, that is, it is in accordance with Article 32. of the Law, if it is signed with a manufacturer for whom a valid manufacturing authorisation has been submitted, or if all the facts listed below can be established:

- The Contract on Representation has been concluded with a legal entity named XY at an address for which it does not have a manufacturing authorisation;
- As part of the same Contract, the manufacturer that releases the medicinal product on the market in Bosnia and Herzegovina with the same name XY, but with a different address for which a valid manufacturing authorisation is enclosed, is specified;
- As part of the Decision of the Ministry of Foreign Trade and Economic Relations, a legal entity named XY with an address for which a manufacturing authorisation is not

enclosed is specified as a signatory, as well as a manufacturer that releases the medicinal product on the market in BiH with the same name XY and an address for which a valid manufacturing authorisation is enclosed;

- A declaration of the legal entity named XY of the signatory of the Contract on Representation has been submitted, that the manufacturer of the name XY with the address from which the medicinal product comes to the BiH market and which is stated on the Contract on Representation, on the Decision of the Ministry of Foreign Trade and Economic Relations and on the enclosed valid manufacturing authorisation, belongs to it.

Alternatively (when the address from which the Contract on Representation is signed and the address for which there is a valid manufacturing authorisation and from which the medicinal product comes to the BiH market, do not have the same name XY as described above) the submitted Contract on Representation is accepted if the following is fullfilled:

- As part of the Contract on Representation and as part of the Decision of the Ministry of Foreign Trade and Economic Relations, all the manufacturing sites from which medicinal products come to the BiH market are listed;
- Valid manufacturing authoprisations have been submitted for all listed manufacturing sites from point a);
- All listed manufacturing sites from point a) belong to the same concern, whose office is a signatory of the Contract on Representation;
- Along with the Contract on Representation, a document from the competent state institution (excerpt from the court register) stating that the office that does administrative work and that has concluded the Contract on Representation, belongs to the same legal entity to which all the manufacturing sites from which medicinal products come to the BiH market and which are listed as part of the Contract on Representation and the Decision of the Ministry of Foreign Trade and Economic Relations, and for which there are valid manufacturing authorisations, has been submitted.

114. Insurance policy for the manufacturer's liability for possible damage caused to the user of the medicinal product, which is valid on the territory of Bosnia and Herzegovina

It is necessary to submit an insurance policy for the manufacturer's liability for possible damage caused to the user of the medicinal product, which is valid for the territory of BiH and which /is:

- within the validity period (the submitted policy has expired),
- issued by an insurance company from BiH,
- in one of the languages that are in official use in BiH,
- covers medicinal products that are the subject of representation (*note: the concerned shall be requested in the event that medicinal products are listed on the policy),
- contains the manufacturer's liability, that is, it contains information that it refers to the manufacturer's liability insurance for possible damage caused to the user of the medicinal product,
- states the manufacturer of the medicinal product, which is a contractual party in the enclosed Contract on Representation, and which is stated in the enclosed Decision of the Ministry of Foreign Trade and Economic Relations and on the submitted application.

1212. A copy of the European Pharmacopoeia certificate for the active substance (CEP)

- A valid CEP with completed information in the *"declaration of access"* section must be provided.
- The valid CEP should contain information on the active substance manufacturing sites; the information provided should be in accordance with the information on the reported active substance manufacturing sites as part of the documentation enclosed to the application concerned.
- In a situation where the proposer submits a CEP where several manufacturing sites of the active substance are approved, and only one manufacturing site of the active substance from the observed CEP appears within the *Flowchart* and Module 3, it is necessary to submit a declaration by the *QP* of the manufacturer of the finished medicine stating that, in the manufacture of the finished medicine, solely the active substance of one of the manufacturers listed on the enclosed CEP, which is indicated in the enclosed *Flowchart* and as part of Module 3, is used. Along with the declaration, valid documents

(manufacturing authorisation + GMP) only for the selected manufacturer of the active substance must be provided.

In case the CEP does not exist, a *Letter of Access* is submitted. The *Letter of Access* document is not required in the following cases:

- ✍ the manufacturer of the active substance and the finished medicine are the same **and**
- ✍ a declaration from the manufacturer concerned on providing us with complete documentation on the active substance as part of M3 has been submitted..

1213. Certificate of the European Pharmacopoeia on the safety of the use of substances with regard to the transmission of transmissible spongiform encephalopathy (TSE/BSE certificate Ph.Eur)

A TSE/BSE Ph.Eur certificate or a certificate that the product does not contain substances of animal origin in accordance with the *template* that is an integral part of this guide must be provided.

1214. Certificate of Pharmaceutical Product (CPP)

- ✍ The submitted certificate of a pharmaceutical product (CPP) must contain information for the proposed medicinal product.
- ✍ CPP must be issued by the competent authority in the country where the manufacturing site of the medicinal product is located.
- ✍ If the CPP is issued by the European Medicines Agency (for medicinal products approved by a centralised procedure), the following must be met:

a) It is stated on the certificate that it is issued for BiH and the manufacturing sites (including the manufacturing site from which the medicinal product comes to the BiH market) are the same ones as those mentioned on the *Flowchart*, on the application and in Module 3.

b) In case that the above-mentioned sites are not the same, and the *CPP* has been issued for Bosnia and Herzegovina, it should be requested that the EMA issues a *CPP* on which the manufacturing sites that are also listed in the application, on the *Flowchart* and Module 3, will be listed.

c) If the above under point b) cannot be submitted, then ask for a *CPP* from the regulatory body from the country of the manufacturer that releases the medicinal product on the market in BiH

1221. Certificate of GMP compliance of a manufacturer which must not be older than three years, for all manufacturing sites

- ✍ *GMP* Certificate must be valid (usually not older than 3 years).
- ✍ *GMP* Certificate must be submitted for all manufacturing sites of the finished medicinal product listed on the *Flowchart*, including the manufacturer of active substance.
- ✍ *GMP* Certificate for the manufacturer must include the manufacturing phase for which, according to the submitted documentation, the manufacturer is responsible.
- ✍ If the submitted *GMP* is a printout from the *EUDRA GMP* database, it is necessary to submit a declaration from the person responsible for placing the medicinal product on the market on the authenticity of the submitted *GMP* certificate with the original.

1222. Manufacturing authorisations for all reported manufacturing sites of the medicinal product (the authorisation must not be older than 5 years)

- ✍ The manufacturing authorisation must be valid and not older than 5 years;
- ✍ The manufacturing authorisation must be submitted for all manufacturing sites of the finished medicinal product listed on the *Flowchart* (application and Module 3), including the manufacturer of active substance.
- ✍ It is necessary that the manufacturing authorisation specifies a related pharmaceutical form in relation to the one proposed in the procedure concerned for granting a marketing authorisation for a medicinal product.

**related pharmaceutical form is that form which according to standard pharmaceutical terms belongs to the same group of forms (eg solid pharmaceutical forms for oral use excluding modified release pharmaceutical forms).*

- ✍ In the event that the manufacturing authorisation is in one of the languages that are not officially used in BiH or English, it is necessary to submit the manufacturing

authorisation translated by an authorised court interpreter into one of the languages that are in official use in BiH or in English.

- ✍ If the submitted marketing authorisation is a printout from the relevant base (it is without signature and seal), it is necessary to submit a declaration from the person responsible for placing the medicinal product on the market on the authenticity of the submitted manufacturing authorisation with the original.

1223. Schematic representation of all manufacturers involved in the manufacture of the finished medicine, starting from the active substance to the finished medicine, specifying which part of the manufacture they perform – *Flowchart*

- ✍ A *Fllowchart* specifying all manufacturing sites of the finished medicinal product and active substance must be provided. It is necessary that the information specified in the *Fllowchart* be in agreement with the information specified in Module 3, in parts 3.2.S.3.1 and 3.2.P.3.1, and the information specified in the application.
- ✍ The *Fllowchart* should be prepared according to the *Template* that is an integral part of this guide.

1224. A declaration by the manufacturers of the finished medicinal product on ensuring that any information about any change in the manufacture or quality of the active substance has been provided to them

Only the declaration by the manufacturer of the finished medicinal product is acceptable, not the declaration by the active substance manufacturer or the declaration by the marketing authorisation holder or any other manufacturer from the *Fllowchart.*

123. Chronological list of approved variations and emergency safety measures in BiH in the period from the date of granting or the last renewal of the marketing authorisation for a medicinal product until the date of submission of the application FOR MARKETING AUTHORISATION RENEWAL

- ✍ A chronological list of approved variations and emergency safety measures in Bosnia and Herzegovina in the period from the date of granting or the last renewal of the marketing authorisation for a medicinal product until the date of submission of the application for marketing authorisation renewal must be provided.

1231. Copy of approved or reported variation - FOR AUTHORISATION RENEWAL

- ✍ It is necessary to submit copies of approved or reported changes in the period from the date of granting or the last renewal of the marketing authorisation until the date of submission of the application for renewal of the authorisation.

Note: In the case of medicinal products that have been granted a marketing authorisation on the basis of Articles 32 and 33 of the Ordinance, in the process of the authorisation renewal, the proposer should submit a list of all reported, approved and unapproved changes in the EU in the period from the issuance of the authorisation for BiH until the submission of the application for authorisation renewal in Bosnia and Herzegovina.

131. and 132. Proposal of SmPC and PIL for BiH in one of the languages that are in official use in BiH, signed by the person responsible for placing the medicinal product on the market

- ✍ The proposal of SmPC and PIL for BiH in one of the languages that are in official use in BiH, signed by the person responsible for placing the medicinal product on the market (it is also necessary to submit the *Word* version of the document) must be submitted.
- ✍ In the enclosed proposal of SmPC and PIL for BiH, it is necessary to specify the temperature range or the highest allowed temperature for storing the medicinal product expressed in degrees °C, in accordance with the requirements of the Ordinance, Appendices IV and V.
- ✍ In the proposal of SmPC and PIL, the indication area or dosage for strengths and forms that are not the subject of the application for granting/renewal of the marketing authorization for a medicinal product should not be specified.
- ✍ In the case of an application for a generic medicinal product, it is necessary to harmonise the submitted SmPC and PIL for BiH with the last approved reference medicine documents concerned.
- ✍ For applications with bibliographic data, it is necessary to harmonise the submitted proposal of SmPC and PIL for BiH with the bibliographic data submitted in Modules 4 and 5.

133. and 134. Proposal of the text of the outer and immediate packaging of the medicinal product or a *Mock-up* with information prescribed by the provisions of the Ordinance and the Law

- ✍ It is necessary to indicate the storage temperature of the medicinal product on the outer packaging (if the storage temperature of the medicinal product is below 25°C).
- ✍ It is necessary to submit a proposal for the outer packaging of the medicinal product, which is prepared in accordance with the provisions of Article 8 of the Ordinance on the content and manner of labeling the outer and immediate packaging of the medicinal product ("Official Gazette of BiH", No. 40/10), i.e., information about the medicinal product on the outer packaging of the medicinal product must be given in the following order: name of the medicinal product, strength, pharmaceutical form and INN.
- ✍ The pharmaceutical form should be in accordance with the valid standard pharmaceutical terms, available on the internet presentation of this Agency.
- ✍ It is necessary to submit a proposal for a *Mock-up* of the outer packaging of the medicinal product without the specified information related to the previously valid authorisation, that is, without the date and number of the decision that is subject to renewal. In the process of granting a marketing authorisation for a medicinal product, the proposal of the text of the outer and immediate packaging is acceptable.
- ✍In the event that the medicinal product contains a combination of a medicinal product and a medical device that enables the administration of the medicinal product and together with it forms a complete product, it is necessary to submit the CE mark for that medical device.
- ✍If the medicinal product has passed the CP procedure, and the procedure here is conducted in accordance with Articles 32 and 33 of the Ordinance, then the composition of the proposed packaging for BiH should be identical to the one approved for the EU and published on the EMA website.

135. The last approved SmPC and PIL by an EU member state, if the medicinal product has been authorised in one of the EU countries

It is necessary to submit a Declaration that the submitted SmPC and PIL are the latest ones authorised in the EU (it is also necessary to specify the EU member state which has approved the documents concerned).

In the case of an **application for a generic medicinal product**, the following must also be submitted:

- A declaration that the submitted **SmPC and PIL of the reference medicinal product** are the latest authorised.
- It must be clear in the documentation that the enclosed latest authorised SmPC and PIL of the reference medicinal product refer to the same reference medicinal product with which the formulation of the generic medicinal product was developed and biological equivalence was confirmed. If they are not taken from the same market, it is necessary to submit an additional declaration by the person responsible for placing the medicinal product on the market that the reference medicinal product on the market from which it was taken for the development of the generic medicinal product concerned has the same qualitative and quantitative composition as on the market from which it was taken for harmonisation of SmPC and PIL and to have the same or related MAH.

136. Proposal of packaging with *Braille*

- It is necessary to submit a packaging proposal with the name of the medicinal product in Braille, in accordance with Article 16 of the Ordinance and a "Declaration on the accuracy of the information specified in Braille on the packaging of the medicinal product", signed by the person responsible for placing the medicinal product on the market (declaration form is Annex 2 of the document "Guide for completing the documentation in the process of renewing a marketing authorisation for a medicinal product ", which is available on the internet presentation of this Agency)*. It is recommended that the accuracy of the information in the above-mentioned statement be verified by a federation, association or institution for the blind and partially sighted people, officially registered in BiH.

14. Information on experts for the assessment of the component parts of the documentation (biographical and bibliographic data, connection with the proposer and expert's signature), namely: **141) Information on the quality expert** **142) Information on the expert for the non-clinical part of the documentation** **143) Information on the expert for the clinical part of the documentation**
✍ For the experts who have conducted the assessment of quality, non-clinical and clinical part of the documentation, it is necessary to submit biographical and bibliographic data and their connection with the proposer. Appointed experts must be those who are signatories of the expert reports in Module 2 (2.3, 2.4 and 2.5).
151. Information for an application with complete documentation (with bibliographic data or with a reference to the documentation of the reference medicinal product) **152. Information related to an application for a generic medicinal product, an application for a hybrid medicinal product, an application for a biosimilar medicinal product**
It is necessary to submit a valid and adequate explanation substantiating the selected type of application. In bibliographic documentation, the long-term use of the medicinal product should be clearly indicated and substantiated. When applying for a generic medicinal product/hybrid medicinal product /similar biological medicinal product, the following conditions must be met: a) The reference medicinal product specified in the application must be the same one with which the SmPC and PIL of the generic/hybrid/biosimilar medicinal product is harmonised; b) The reference medicinal product from the previous point must be identical to: - the reference medicinal product in Module 3 (3.2.P.2) with which the medicinal product was developed;

- the reference medicinal product in Module 5 (5.3.1), that is, in Module 2.5, with which the biological equivalence of the reference and generic/hybrid/biosimilar medicinal product has been confirmed.

c) The reference medicinal product must be from the market belonging to the EEA zone.

153. Information on data exclusivity

From 30 July 2021, in Bosnia and Herzegovina, the provision from Article 34, paragraph 1, point c) of the Law, which refers to data exclusivity (period of data exclusivity), applies.

Specific documentation related to the safety of medicinal product administration

181. Description of the pharmacovigilance system in BiH

- ✍ A description of the pharmacovigilance system, which refers to BiH and which is signed by the appointed person responsible for pharmacovigilance must be provided.
- ✍ For manufacturers outside Bosnia and Herzegovina, the proposer is also obliged to submit a description of the global pharmacovigilance system developed by the manufacturer and a description of the marketing authorisation holder's local pharmacovigilance system signed by the appointed person responsible for pharmacovigilance.

182. Risk management plan (RMP), when there is a necessary risk management plan that the applicant plans to implement in BiH

- ✍ The risk management plan must be submitted in accordance with the guide for the risk management plan published by this Agency.

Periodic Safety Update Report (PSUR)

- ✍ The latest available PSUR, which includes data collected from all markets where the medicinal product in question is present, must be provided. If the PSUR does not exist, because the medicinal product has not been previously approved anywhere or for some other reason, the proposer is obliged to submit a declaration that they do not have a PSUR with an explanation for the non-existence (the declaration should be signed by the PV person of the manufacturer that releases the medicinal product on the market in BiH and the responsible person for medicinal product registration).

- ✍ In the authorisation renewal procedure, it is necessary to submit the PSUR (section 5.3.6. of Module 5), which includes data on experiences after placing the medicinal product on the market (data on the medicinal product collected during the period of validity of the authorisation that is subject to renewal). The date of the final data must not be older than 60 days from the date of submission of the application for renewal in BiH).

Specific documentation if the procedure is based on Articles 32 and 33 of the Ordinance

172. Assessment Report

- ✍ A Final Assessment report related to the medicinal product in question along with its annexes (if any) must be provided.

173. EU authorisation (EU Decision)

- ✍ The EU authorisation / decision related to the medicinal product in question along with its annexes (if any) must be provided.

174. A declaration that the submitted documentation is identical to the documentation that was attached to the EMA for CP or the reference state for DCP or MRP

✍A declaration from the person responsible for placing the medicinal product on the market that the submitted documentation is identical to the documentation that was enclosed to the EMA for CP or the reference state for DCP or MRP procedures must be provided.

- ✍ The person responsible for the registration of medicinal products is obliged to submit a list of all changes that occurred in the period from the issuance of the European decision/authorisation to the submission of the application for granting a marketing authorisation for a medicinal product in Bosnia and Herzegovina. Along with the list, it is necessary to enclose the approvals of those changes and all the documentation on the basis of which the changes were approved (these documents should technically be submitted as part of Module 1, as *an additional document*, specifying a more precise name of the document). In the event that it has been more than 5 years since the issuance of the authorisation in the EU, which was the basis for the shortened procedure in BiH, then the submission of the *Addendum report*, the one that was enclosed in the EU when the authorisation was renewed, should be requested.

175. A declaration that the medicinal product marketed in BiH is identical and with the same manufacturing and releasing on the market site as the medicinal product marketed in the EU
✍ A declaration from the person responsible for placing the medicinal product on the market that the medicinal product marketed in BiH is identical and with the same manufacturing and releasing on the market site as the medicinal product marketed in the EU must be provided.
2.4 Expert's report on preclinical documentation (*Non-clinical Overview*) or report with all addendums to the expert's report (*Addendum report*)
✍ The report (or *Addendum report*) enclosed in part 2.4 must be dated. The date of the final data must not be older than 60 days from the date of submission of the application for renewal in BiH. It must be signed by the appointed expert.
2.5. Expert's report on clinical documentation (*Clinical Overview*) or report with all addendums to the expert's report (*Addendum report*)
✍ The report (or *Addendum report*) enclosed in part 2.5 must be dated. The date of the final data must not be older than 60 days from the date of submission of the application for renewal in BiH. It must be signed by the appointed expert.

Do not insert unnecessary documents. Certificates, manufacturing authorisations of intermediaries, excipients, etc. are often submitted ... and these are unnamed documents documents, which further complicates and prolongs the assessment.

Along with the printed version of the Application (signed and stamped), submit the PIL and SmPC proposals signed by the person responsible for the registration of medicinal products.

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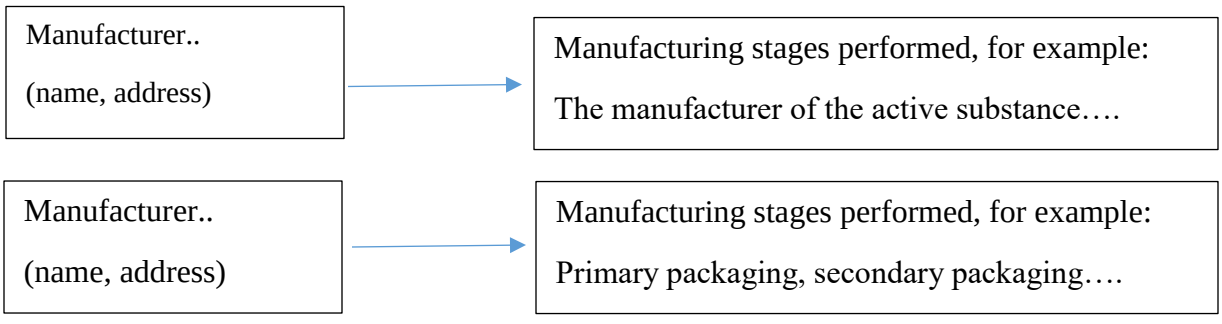
FOR HIGHER QUALITY PREPARATION OF REGISTRATION DOCUMENTATION (MODULE 1)

***Flowchart* template**

The manufacturers' addresses should be listed as on the corresponding GMP certificates and manufacturing authorisations.



Template for Confirmation that the product does not contain substances of animal origin

Naziv pravnog lica

Adresa

Datum:

Izjava proizvođača glede upotrebe materijala humanog ili životinjskog porijekla uključujući supstannce koje nose rizik od animalne spongiformne encefalopatije

☐ Mi, (pravno lice iz naslova dokumenta) ovim potvrđujemo da materijali koji se koriste u proizvodnji aktivne supstane/gotovog lijeka (navesti naziv) nisu životinjskog ili humanog porijekla.

(staviti krstić u kvadratić ukoliko je izjava tačna/primjenjiva)

Name of legal entity

Adress

Date:

Letter of declaration of manufacture regarding the use of material of human or animal origin including substances at risk of transmitting agents of animal spongiform encephalopathies

☐ *We, (name of legal entity) hereby confirm that materials used in the manufacturing process of (name of active substance or name of medicinal product) are not of human or animal origin.*