Pursuant to the Article 7 paragraph 1 item 3 and Articles 16, 17a, 18, 21 and 22 of the Law on Medicines ("Official gazette of the RoM“, no. 80/04 and "Official gazette of Montenegro", no. 18/08), Ministry of Health and Social Care adopts

Rulebook on More Detailed Conditions for Issuance of Marketing Authorisation for a Medicine

Rulebook has been published in the “Official gazette of Montenegro“, no. 30/2009 from 28.4.2009

I GENERAL PROVISIONS

Article 1

The Rulebook defines more detailed conditions for issuance of marketing authorisation for a medicine, contents of the application and necessary documents for obtaining marketing authorisation, contents of the marketing authorisation for a medicine, conditions, manner and necessary documents for amending and supplementing marketing authorisation, as well as the contents of documents necessary for renewal of marketing authorisation for a medicine.

Article 2

Terms used in this Rulebook have the following meaning:

1) centralised authorisation procedure is European procedure for issuance of authorisation, which is in the competence of European Medicines Agency (EMEA) pursuant to the Regulation (EC) no. 726/2004;

2) decentralised authorisation procedure is European procedure for obtaining marketing authorisation for a medicine, which starts at the same time in the reference country and other EU Member States, which are involved in the procedure;

3) mutual recognition procedure is European procedure for obtaining marketing authorisation for a medicine, which, after the approval in the referent EU Member State, is also approved by other EU Member States, which are involved in the procedure;

4) national procedure is a procedure for obtaining marketing authorisation for a medicine in Montenegro;

5) reference EU Member State is a country, which prepares and issues Assessment Report in the decentralised authorisation procedure or in the mutual recognition procedure;

6) Assessment Report is a document in which EMEA or competent authority of EU Member State reports based on expert reports about quality, safety and efficiency of the medicine, and based on that suggests issuance of marketing authorisation for a medicine or rejection of issuance.

II CONDITIONS FOR ISSUANCE OF MARKETING AUTHORISATION FOR A MEDICINE

Article 3

Marketing authorisation for a medicine may be issued to the applicant for marketing authorisation, referred to in the Article 13 paragraph 3 of the Law on Medicines, based on application and documents stipulated by this Rulebook.

a) Contents of the Application

Article 4

Application for issuance of marketing authorisation for a medicine, shall contain:

1) supporting letter for issuance of authorisation;

2) completed application form for issuance of authorisation;

3) documents on medicine which is stipulated by this Rulebook, and

4) proof that all the stipulated fees are paid.

Application referred to in the paragraph 1 item 2 of this Article, shall be submitted for all pharmaceutical forms, and strength of the medicine and packaging, at the form, which is printed with this Rulebook and represents its integral part (Annex 1).

Applicant for marketing authorisation shall submit the medicine samples necessary for laboratory quality control of the medicine, upon request of the Agency for Medicines and Medical devices (hereinafter: Agency).

Article 5

Supporting letter referred to in the Article 4 paragraph 1 item 1 of the Rulebook, shall contain:

- logo, name and address of the applicant;
- subject of the application;
- data on medicine (international non-protected name of the medicine (INN) or generic name, pharmaceutical form and strength of the medicine), which have to be identically stated in the documents and at the form;
- proposal of packaging of the medicine and/or data on packaging of the medicine,
- data on manufacturer of the medicine (name, address and manufacturing site);
- proposal of ATC (Anatomical-Therapeutic-Chemical) classification code, or ATC veterinary classification code for medicinal product for veterinary use;
- proposal of regime of issuing of a medicine (prescription only, or non-prescription medicine), and
- date and signature of person responsible for the procedure of issuance of the authorisation.

Supporting letter referred to in the paragraph 1 of this Article, may also refer to more applications for marketing authorisation, in which case all applications shall be clearly mentioned.

Article 6

Application for marketing authorisation for a medicine referred to in the Article 4 of this Rulebook shall be submitted to the Agency.

Agency shall determine if the application is complete and inform the applicant in written form thereof, within 30 days from the day of submission of the application.

If the Agency determines that the application is not complete, it shall inform the applicant to submit the stipulated data within 30 days from the day of receipt of the notification.

If the applicant does not submit requested data within the period defined in the paragraph 3 of this Article, the Agency shall reject the application for authorisation as incomplete.

b) Necessary documents

Article 7

Documents referred to in the Article 4 paragraph 1 item 3 of this Rulebook, shall contain:

1) **application with complete own documentation**

- own data on pharmaceutical-chemical-biological testing of the medicine;
- own data on pre-clinical i.e. pharmacological and toxicological examination of the medicine and
- own data on clinical trial of medicine containing all stipulated parts;

2) **application with bibliographic data:**

- own data on pharmaceutical-chemical-biological testing of the medicine;
- bibliographic data on pre-clinical i.e. pharmacological and toxicological examination of the medicine, and
- bibliographic data on clinical trial of medicine containing all stipulated parts;

3) **application with combined data:**

- own data on pharmaceutical-chemical-biological testing of the medicine;
- combined i.e. partially own, partially bibliographic data on pre-clinical i.e. pharmacological and toxicological examination of the medicine, and
- combined i.e. partially own, partially bibliographic data on clinical trial of medicine containing all stipulated parts;

4) **application for generic medicine, for which a shortened documentation is submitted:**

- own data on pharmaceutical-chemical-biological testing of the medicine;
- referring to data on pre-clinical i.e. pharmacological and toxicological examination of the reference medicine;
- referring to data on clinical trial of reference medicine;

- proof of essential similarity of reference medicine and medicine for which the application for marketing authorisation is being submitted;

- proof that the reference medicine is on the market at least eight years in Montenegro or in other countries which have the same professional requests for obtaining marketing authorisation for a medicine;

5) **application with reference to the documentation of the reference medicine:**

- references to documentation about pharmaceutical-chemical-biological testing of the reference medicine, about pre-clinical i.e. pharmacological-toxicological examination of the reference medicine and/or clinical trial of the reference medicine;

- proof that the holder of the marketing authorisation for the reference medicine agrees with reference to his documentation regarding the pharmaceutical-chemical-biological testing of the reference medicine, about pre-clinical i.e. pharmacological-toxicological examination of the reference medicine and/or clinical trial of the reference medicine;

6) **application for biologically similar medicine which does not fully comply with the term generic medicine:**

- own data on pharmaceutical-chemical-biological testing of the medicine i.e. on the quality of the medicine;

- reference to data on pre-clinical i.e. pharmacological-toxicological examination of the reference medicine and data or results of appropriate pre-clinical i.e. pharmacological-toxicological testing of the medicine which refer to the differences when compared to the reference medicine;

- reference to data on clinical trial of the reference medicine and data or results of appropriate clinical trials of the medicine which refer to differences in comparison to the reference medicine;

7) **application for medicine which contains the fixed combination of active substances:**

- own data on pharmaceutical-chemical-biological testing of the medicine i.e. on the quality of the medicine;

- data on pre-clinical i.e. pharmacological-toxicological examination of the medicine;

- data on clinical trial of the medicine.

If the application for authorisation refers to the medicine which contains fixed combination of active substances, which are all already separately a part of the composition of medicines that already possess the authorisation for Montenegro or other countries which have the same professional requirements for obtaining the marketing authorisation for a medicine, it is only necessary to submit data on fixed combination, and not on each active substance separately.

Article 8

For issuance of marketing authorisation for a medicine, apart from conditions stipulated in the Article 7 of this Rulebook, it is necessary to meet the following conditions, namely:

1) bibliographic data referred to in the Article 7 item 2 and 3 of this Rulebook, may be used only with the proof that the active substance is being used as a medicine for at least ten years in Montenegro or other countries which have equally high standards and for which there is published basically harmonised professionally acknowledged literature, which contains all necessary data from requested pharmacological-toxicological documentation or clinical documentation;

2) shortened documentation for generic medicine referred to in the Article 7 item 4 of this Rulebook, may be used only with the evidence that the reference medicine is on the market for at least eight years in Montenegro or other countries, which have the same professional requirements for obtaining marketing authorisation for medicine and the marketing authorisation shall not be issued before the expiry of period of ten years from the issuance of the first marketing authorisation for the reference medicine, and

3) reference to the documentation on pharmaceutical-chemical-biological testing of the reference medicine, shall be used only if the reference number possesses marketing authorisation of medicine in Montenegro.

Article 9

Documentation referred to in the Article 4 paragraph 1 item 3 of this Rulebook, shall be submitted in the form of:

1) common technical document (hereinafter: CDT file), which shall refer only to medicinal products for human use, or

2) European (EU) file, which refers to:

a) medicinal products for human use and are only used if the authorisation has already been issued in the EU based on such file, until 01.01. 2010. Since 01.01. 2010, documentation in the form of EU file shall be submitted only in cases when applicant cannot present medicine in CDT file, and the Agency decides that the medicine is of importance for health protection,

b) medicinal products for veterinary use, and

c) immunobiological veterinary medicines.

Article 10

CDT file shall contain the following parts:

Module 1 – Administrative and regional data;

Module 2 – Concise expert presentations of Modules 3, 4 and 5;

Module 3 – Data on quality (pharmaceutical-chemical-biological data);

Module 4 – Pre-clinical (pharmacological-toxicological) examination, and

Module 5 – Clinical trials.

Article 11

EU file shall contain the following parts:

I part: administrative data i.e. documentation;

II part: pharmaceutical-chemical-biological documentation;

III part: pharmacological-toxicological documentation for medicinal products for human use or

- documentation on examination of residue or testing of the safety of veterinary medicinal products or
- documentation on examination of residue or testing of the safety of immunobiological veterinary medicinal products.

IV part:

- clinical documentation for medicinal products for human use, or
- documentation on pre-clinical and clinical examination of efficiency of veterinary medicinal products, or
- documentation on examination of efficiency of immunobiological veterinary medicinal products.

Article 12

Modules 1 and 2 referred to in the Article 10 of this Rulebook, shall be submitted, as a rule, either in paper or electronic format.

Modules 3, 4 and 5 referred to in the Article 11 of this Rulebook, shall be submitted, as a rule, in electronic format, and upon request of the Agency some parts shall be submitted in the paper format.

Parts II, III and IV referred to in the Article 11 of the Rulebook, may be submitted in paper or electronic format.

Documents and certificates which are being submitted within the module 1 CTD and Part 1 of EU file, may be submitted:

- as original documents;
- as authorised copies, or
- as photocopies with the statement of the applicant on their authenticity.

Article 13

Structure of CTD shall be in accordance with the Commission Directive 2001/63/EC

Detailed description of the structure of CTD and EU file is printed together with this Rulebook and represents its integral part (Annex 2 and Annex 3).

III CONTENTS OF THE AUTHORISATION

Article 14

Marketing authorisation for a medicine shall contain:

1. logo, name and address of the Agency;
2. data on holder of the authorisation;
3. data on manufacturer;
4. name of the medicine (protected, international non-protected name (INN) or generic name);
5. pharmaceutical form, strength and packaging of the medicine;
6. qualitative and quantitative composition of active substance;

7. anatomical-therapeutical-chemical classification code for medicine (ATC), or anatomical-therapeutical-chemical veterinary classification code for medicine (ATC-vet);
8. EAH identification code of products (13 or 8 numbers);
9. regime of issuing of a medicine;
10. information on contents of narcotic or psychotropic substances and stipulated mark for that type of medicines, if necessary;
11. number and date of authorisation;
12. period for which the authorisation is being issued;
13. signature of responsible person in the Agency, and
14. law of remedies.

Integral part of the authorisation referred to in the paragraph 1 is:

- approved summary of basic characteristics of the medicine with the regime of issuing of a medicine and date of last approved version, which is printed with this Rulebook and represents its integral part (Annex 4),
- approved instruction for patient or user with the regime of issuing and date of last approved version, in accordance with the act which regulates labelling of medicine, and
- approved immediate and outer packaging or its approved conceptual design or approved label, in accordance with the act which regulates labelling of medicines.

IV CONDITIONS, MANNER AND NECESSARY DOCUMENTS FOR AMENDING AND SUPPLEMENTING MARKETING AUTHORISATION

Article 15

Holder of the authorisation, according to the Law, is obliged to follow scientific and technical development, pharmacovigilance and other data on medicine, informs Agency about the estimate of quality, safety and efficiency of the medicine, and reports about the change, i.e. submits a request for amendments and supplements to the authorisation (hereinafter: variations), in accordance with the new findings about the medicine.

Article 16

Variations referred to in the Article 15 of this Rulebook are:

1) smaller variations – variations of the type I which may be variations type IA and variations type IB;
2) larger variations – variations type II, and
3) variations for which a new authorisation should be issued, which represents expending of the scope of the existing authorisation, based on the new request.

Article 17

Smaller variations of the type IA and variations of the type IB refer to changes stated in the List of Variations, which is printed with this Rulebook and represents its integral part (Annex 5).

Exceptionally, variations type IA and IB which refer to certain variations of immunological medicines, medicine from blood and plasma, radio-pharmaceutical medicines and bio-technological medicines shall be processed upon request for variations type II.

Article 18

Larger variations – variations of the type II are variations which do not belong to variations type I nor the variations for which a new authorisation should be issued based on the new request.

Variations type II refer to:

- changes of administrative data;
- changes of pharmaceutical-chemical-biological part of documentation,
- changes of pharmacological-toxicological part of documentation, and
- changes which lead to changes in summary of basic characteristics of the medicine, instructions for use of the medicine and packaging of the medicine.

Application form for type IA and IB and as well as the request for introduction of the variation type II is printed with this Rulebook as its integral part (Annex 6).

Article 19

Variations for which it is necessary to amend the authorisation based on new application for marketing authorisation for a medicine, refers to changes which are stated in the List of Variations which is printed with this Rulebook as its integral part (Annex 7).

Article 20

Complete application of variation/s or request for approval of variation/s shall contain:

1) supporting letter of the holder of the authorisation;
2) completed form for variations,
3) documentations which refers to variation and which provides sufficient data for its evaluation and
4) proof that all the stipulated fees are paid.

Article 21

Supporting letter referred to in the Article 20 paragraph 1 item 1 of this Rulebook, shall contain:
- logo, name and the address of the holder of the authorisation;
- request or application for approval of variations with stated variation;
- name of the medicine (protected, international non-protected name (INN) or generic name, pharmaceutical form, strength of the medicine). Identical data shall be stated in the documentation and on the form;
- packaging of the medicine;
- name of the manufacturer of the medicine,
- planned date of introduction of the variation and
- date and signature of the person in charge for submission of request or application.

Supporting letter refers only to one variation, except in the case of consequential variations, when the supporting letter refers to all variations in which case all requests shall be clearly mentioned.

Article 22

Holder of the authorisation shall report the variation to the Agency or submit the request for approval of the variation.

Agency evaluates if the application or request for approval of variation is complete and informs the holder of the authorisation thereof.

If the application or request is complete, period for evaluation procedure of the application or request shall commence on the date of reception of the notification referred to in the paragraph 2 of this Article, in accordance with the Law.

Holder of the authorisation referred to in the paragraph 1 of this Article, shall inform the Agency on the date of introduction of variation.

Article 23

If the application, or request is not complete, the Agency shall inform the holder of the authorisation in written form and request that the application or request is amended.

If the application or request is not amended within 30 days, it shall be rejected as incomplete.

Period referred to in the paragraph 2 of this Article shall commence on the day when the holder has received the notification referred to in the paragraph 1 of this Article.

Article 24

Documentation for variations for which a new authorisation should be issued based on the new request, shall consist of all parts of the application for marketing authorisation for a medicine.

Holder of the authorisation, instead of repeated submission of previously submitted documentation on medicine, may refer to the reference and to previously submitted documentation for issuance of authorisation.

Article 25

Agency may reject with explanation the request for variation within 15 days from the day of reception of complete request for variation type IA.

Agency may reject with explanation the request for variation within 30 days from the day of reception of complete request for variation type IB.

Agency may reject with explanation the request for variation or approve introducing of the variation within 60 days from the day of reception of complete request for variation type II. In special cases according to the professional estimation of the Agency, this period may be prolonged up to 90 days.

Agency may issue decision on rejection of the request with explanation or approve issuance of new authorisation within 210 days from reception of complete request for introduction of variation for which a new authorisation should be issued based on the new request, which represents expending of the scope of the existing authorisation

Article 26

Holder of the authorisation shall inform immediately the Agency about the urgent safety measures, which refer to certain restrictions in indications of the medicine, change in dosing, adding of contraindications and adverse reactions in the summary of basic characteristics of the medicine and instruction for patients/users or about other forms of restrictions, in order to prevent risks for human health.

If the Agency has no comments on urgent safety measures referred to in the paragraph 1 of this Article, or does not reply to the holder of the authorisation, the holder of the authorisation shall introduce the variation within 24 hours from the moment he submitted the notification to the Agency.

Holder of the authorisation shall submit to the Agency completed form for appropriate variation with necessary documentation immediately after introducing the measure referred to in the paragraph 2 of this Article, the latest within 15 days.

Article 27

The change of the authorisation in this Rulebook shall also refer to the transfer of authorisation from one holder of authorisation to new holder of authorisation.

Request for transfer of authorisation to other legal or private person, shall contain:

1) supporting letter from the current holder of authorisation;
2) completed form for transfer of authorisation;
3) other necessary documentation upon request of the Agency, and
4) proof that all the stipulated fees are paid.

Agency shall render written decision with which it approves the transfer of authorisation to the new holder or reject the request for transfer of authorisation, within 30 days from the day of reception of complete request for amendment of authorisation – transfer of authorisation.

The form referred to in the paragraph 2 item 2 of this Article is printed with this Rulebook as its integral part (Annex 8).

Article 28

Supporting letter of the holder of the authorisation referred to in the Article 27 paragraph 2 item 1 of this Rulebook, shall contain:

- logo, name and address of the holder of the authorisation;
- request for transfer of the marketing authorisation for a medicine;
- data on medicine (protected, international non-protected name (INN) or generic name, pharmaceutical form, strength of the medicine);
- packaging/s of the medicine;
- data on manufacturer of the medicine (full name, address, data on manufacturing site);
- date and number of issued authorisation;
- name and address of the new holder of authorisation and proof that all legal requirements for holder of authorisation have been fulfilled;
- statement of acceptance of responsibilities of the holder of authorisation from the new holder of the authorisation;
- statement of the current holder of authorisation that all documentation necessary for fulfilment of obligations of holder of authorisation shall be submitted to the new holder of the authorisation, and
- date and signature of responsible person.

V RENEWAL OF AUTHORISATION

Article 29

Holder of the authorisation shall submit the application for renewal of the authorisation to the Agency in the period stipulated by the law, and submit the following documentation:

1) supporting letter of the holder of the authorisation;
2) completed form of the application for renewal of the authorisation;
3) documentation of the medicine stipulated by this Rulebook;
4) updated administrative data, and
5) proof that all the stipulated fees are paid.

Upon request of the Agency, the applicant for renewal of authorisation shall submit samples of medicines needed for laboratory quality control.

Application form referred to in the paragraph 1 item 2 of this Article shall be submitted for every pharmaceutical form, strength of the medicine and packaging on the form which is printed with this Rulebook as its integral part (Annex 9).

Article 30

Supporting letter of the holder of the authorisation referred to in the Article 29 paragraph 1 item 1 of this Rulebook shall contain:

- logo, name and address of the holder of the authorisation;
- application for renewal of the authorisation;
- data on medicine (protected, international non-protected name (INN) or generic name, pharmaceutical form, strength of the medicine). Identical data shall be stated in the documentation and on the form;
- packaging/s of medicine;
- data on manufacturer of medicine (full name, address, data on the manufacturing site);
- date and number of issued authorisation, and
- date and signature of responsible person.

Supporting letter referred to in the paragraph 1 of this Article may refer to more applications for authorisation.

Article 31

Documentation on medicine referred to in the Article 29 paragraph 1 item 3 of this Rulebook shall contain:

1) completed/updated summary of basic characteristics of the medicine;
2) completed/updated instruction for patients i.e. users;
3) proposal of conceptual design or already produced immediate and outer packaging;
4) last Periodic Safety Update Report of medicine (PSUR) or reference to already submitted PSUR in accordance with the harmonised dynamics of submission of PSUR for that medicine, and
5) list of approved and registered variations in the period of validity of authorisation.

On renewal of the authorisation the holder of the authorisation shall submit with separate PSURs also the related report on safety of the medicine (Summary Bridging Report) which covers the period of 4 years and 4 months from the day of marketing of the medicine in Montenegro.

Exceptionally, with written explanation the holder of authorisation may submit instead of Summary Bridging Report additional report (Addendum Report) which refers to the time period from conclusion of the last PSUR.

Addendum Report shall not cover the time period longer than 12 months, and the day of cessation of entering of data shall not be longer than 60 days from the day application for renewal of authorisation was submitted.

Article 32

Updated administrative data referred to in the Article 29 paragraph 1 item 4 of this Rulebook, shall encompass:

- GMP certificate for the manufacturing site stated in the documentation, not older than three years and the statement that the updated GMP certificate shall be submitted to the Agency every three years, and
- other updated data upon request of Agency, if those data have influence on public health.

Article 33

Agency shall perform professional assessment of the documentation on the medicine, after it determines that the application is complete.

In the procedure of professional assessment of the documentation on the medicine, the Agency may ask in written form from the holder of the authorisation who applied for renewal of authorisation, additional information and documentation which are necessary for the estimate of quality, safety and efficiency of the medicine.

If the holder of the authorisation does not submit additional information and documentation referred to in the paragraph 2 of this Article, within 30 days from the day of reception of written notification, the Agency shall reject application for renewal of authorisation.

Article 34

For medicines which received marketing authorisation for a medicine in the centralised procedure of EU, applicant for marketing of the medicine shall submit part I and part II of EU file and module 1, module 2 and model 3 of CTD file referred to in the Article 10 and 11 of this Rulebook, which has been accepted by the EMEA, as well as detailed list of contents of the part III, part IV of EU module 4 and 5 of CTD file.

If the Agency finds it necessary, applicant referred to in the paragraph 1 of this Article, shall submit complete parts of the documentation referred to in the indent 2 of the paragraph 1 of this Article.

VI SPECIAL PROCEDURE FOR OBTAINING, RENEWAL, CHANGES AND AMENDMENTS TO THE MARKETING AUTHORISATION FOR A MEDICINE

Article 35

With the application for obtaining, renewal, changes and amendments to the marketing authorisation for a medicine in a special procedure, pursuant to the Article 17a of the Law on Medicines, beside the documentation referred to in the Articles 7 to 13 of this Rulebook, it is also required to submit:

- Assessment Report on the medicine issued by EMEA or reference Member State for medicines approved according to the centralised procedure, decentralised procedure or mutual recognition procedure;
- list of other Member States which participated in the decentralised procedure or mutual recognition procedure;
- Assessment Report on the medicine issued by a EU Member State in which a marketing authorisation was approved for a medicine according to the national procedure;
- statement of the applicant that the documentation based on which the marketing authorisation for a medicine is required in Montenegro is identical documentation base on which the Assessment Report was drafted and issued, including all changes which were approved by the day of application, and that the submitted documentation is valid in EU Member States;
- statement of the applicant that he/she shall inform without delay the Agency in the case of temporary or permanent revoking of the marketing authorisation for a medicine in the European Union, as well as about all urgent safety measures.

Article 36

Procedure for issuance of authorisation for medicines referred to in the Article 35 of this Rulebook shall not last more than 90 days.

VII REQUEST FOR TERMINATION OF VALIDITY OF AUTHORISATION

Article 37

Holder of the marketing authorisation for a medicine may submit a request for termination of validity of authorisation.

Request referred to in the paragraph 1 of this Article shall contain:

1) supporting letter from the holder of authorisation,
2) completed form for termination of validity of authorisation, and
3) proof that all the stipulated fees are paid.

Form referred to in the paragraph 2 item 2 of this Article is printed with this Rulebook as its integral part (Annex 10).

Agency shall issue the decision on termination of validity of authorisation within 30 days from the day completed application was submitted.

Article 38

Supporting letter referred to in the Article 37 paragraph 2 item 1 of this Rulebook, shall contain:

- logo, name and address of the holder of the marketing authorisation;
- request for termination of validity of authorisation;
- data on medicine (protected, international non-protected name (INN) or generic name, pharmaceutical form, strength of the medicine);
- packaging/s of the medicine;
- data on manufacturer of the medicine (full name, address, data on manufacturing site);
- date and number of issued authorisation,
- reason for termination of validity of authorisation and
- date and signature of responsible person.

Article 39

Requests and documentation stipulated by this Rulebook shall be submitted in the language which is officially used in Montenegro.

In the case from the Article 3 paragraph 1 item 3 and Article 29 paragraph 1 item 3 of this Rulebook, documentation may be submitted also in English language, with the exception of the proposal of summary of basic characteristics of the medicine, proposal of the instruction for patient/user and proposal of immediate and outer packaging of the medicine which shall be submitted exclusively in the language which is officially iced in Montenegro.

VIII TRANSITIONAL AND FINAL PROVISION

Article 40

Rulebook on More Detailed Conditions for Issuance of the Marketing Authorisation for a Medicine ("Official gazette of Republic of Montenegro", no. 54/06) shall cease to have effect when this Rulebook enters into force.).

Article 41

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

Number: 03-787/2

Podgorica, April 22nd 2009

Minister,
Docent **Miodrag Radunović**, MD sgd.

ANNEX 1

Form

Agency for Medicines and Medical Devices of Montenegro

Number of the file:	Received by:
Date of reception:	Date of application with additional documentation:
Date of reception of additional documentation:	Date of complete application:

Filled in by the Agency for Medicines and Medical Devices of Montenegro

APPLICATION FOR ISSUANCE OF MARKETING AUTHORISATION FOR A MEDICINE

☐ Medicinal product for human use

☐ Medicinal product for veterinary use

BASIC DATA (to be filled-in in printed letters)[1]	
Name of the medicine:	
Active substance/s (INN in official language:	
Pharmaceutical form:	
Strength:	
Packaging:	
APPLICANT for marketing authorisation of a medicine	
Name of the company:	
Address:	
RESPONSIBLE PERSON for obtaining the marketing authorisation for a medicine	
Name, surname and title	
Telephone:	

Telefax:	
E-mail:	
MANUFACTURE:	
Name of the company:	
Address:	
Other of manufacturing sites:	
HOLDER OF MARKETING AUTHORISATION for a medicine	
Name of the company:	
Address:	
DATE ON PROCEDURE FOR OBTAINING MARKETING AUTHORISATION FOR A MEDICINE IN EUROPEAN UNION	

☐ **Centralised procedure**

☐ **Decentralised procedure**

Reference country:

Number of the procedure:

Date of issuance of authorisation:

Other Member States in the procedure (fill in the appropriate box in the table according to abbreviation from the list of EU countries):

AT	☐	BE	☐	BG	☐	CY	☐	CZ	☐	DE	☐	DK	☐	EE	☐
EL	☐	ES	☐	FI	☐	FR	☐	HU	☐	IE	☐	IS	☐	IT	☐
LI	☐	LT	☐	LU	☐	LV	☐	MT	☐	NL	☐	NO	☐	PL	☐
PT	☐	RO	☐	SE	☐	SI	☐	SK	☐	UK	☐				

☐ **Mutual recognition procedure**

Reference country:

Number of the procedure:

Date of issuance of authorisation:

Other Member States in the procedure (fill in the appropriate box in the table according to abbreviation from the list of EU countries):

AT	☐	BE	☐	BG	☐	CY	☐	CZ	☐	DE	☐	DK	☐	EE	☐
EL	☐	ES	☐	FI	☐	FR	☐	HU	☐	IE	☐	IS	☐	IT	☐
LI	☐	LT	☐	LU	☐	LV	☐	MT	☐	NL	☐	NO	☐	PL	☐
PT	☐	RO	☐	SE	☐	SI	☐	SK	☐	UK	☐				

List of countries with abbreviations

Abbreviation/Name of the country		Abbreviation/Name of the country		Abbreviation/Name of the country		Abbreviation/Name of the country		Abbreviation/Name of the country	
AT	Austria	DK	Denmark	HU	Hungary	LU	Luxembourg	PT	Portugal
BE	Belgium	EE	Estonia	IE	Ireland	LV	Latvia	RO	Romania
BG	Bulgaria	EL	Greece	IS	Island	MT	Malta	SK	Slovak Republic
CY	Cyprus	ES	Spain	IT	Italy	NL	Netherlands	SL	Slovenia
CZ	Czech Republic	FI	Finland	LI	Liechtenstein	NO	Norway	SE	Sweden
DE	Germany	FR	France	LT	Lithuania	PL	Poland	UK	United Kingdom

☐ **National procedure:**
Country:
Number and date of issuance of authorisation:

TYPE OF APPLICATION (to mark)

☐ ***Application with complete documentation***

☐ ***Application with bibliographic data***

☐ ***Application with combined data***

☐ ***Application with shortened documentation of reference medicine***[2]

☐ ***Generic documentation***

☐ ***Application with own data***

☐ ***Consent of the holder of authorisation***

	Study of bio-equivalence	YES ☐	NO ☐

	Reference medicine	
	Name, strength, form:	
	Manufacturer:	
	Holder of the marketing authorisation for the reference medicine	
	Date of issuance of authorisation in Montenegro	
	Date of issuance of authorisation in EU	
	Date of issuance of authorisation in countries with same applications for marketing authorisation for a medicine	

☐ **Fixed combination**

☐ **Biologically similar medicine**

☐ **Variations for which it is necessary to expand the scope of authorisation based on new application for issuance of marketing authorisation for a medicine:**

Variations which refer to active substance/s:

☐ Additional active substance, including antigens vaccine

☐ Removal of active substance including antigens vaccine

☐ Change of quantity of active substance

☐ New form of active substance (for example: new form of salt, ester and other derivatives, while the structure remains with the same therapeutically effect)

☐ Replacement of active substance with other isomer, other complex, change of recemate with one enantiomer

☐ Replacement of biological substance or biotechnological product with other different molecular structure; change of vector, which is used for making biotechnological material or change of the source of the cell bank

☐ New ligand or binding mechanism with radio-pharmaceutical products

Changes of the strength of pharmaceutical form or way of use of medicine:

☐ Changes of bio-availability

☐ Changes in pharmacokinetics

☐ Additional strength of medicine

☐ Change or addition of new pharmaceutical form of medicine ☐ Addition of new way of use of medicine

DATA ON MEDICINE		
1.	**PROPOSAL OF *ATC* (ANATOMICAL-THERAPEUTIC-CHEMICAL CLASSIFICATION CODE FOR MEDICINE) GROUP, OR *ATC* vet.:**	
2.	**INDICATIONS[3]:**	
2.1	**TARGET KINDS OF ANIMALS, I.E. CATEGORIES (VET)[4]:**	
3.	**WAY OF USE:**	
4.	**PACKAGING[5]**	
	Immediate packaging:	
	Outer packaging:	
	Quantity of pharmaceutical form in immediate packaging:	
	Quantity of immediate packaging in outer packaging:	
	Additional equipment, or medical devices:	
5.	**SHELF LIFE:**	
5.1	**SHELF LIFE** (after first opening of original packaging):	
5.2	**SHELF LIFE** (after reconstitution or dilution):	
5.3	**SHELF LIFE** (after mixing of premix in food): (VET.)	
6.	**STORAGE CONDITIONS:**	

7.	**PROPOSAL OF REGIME OF ISSUING:** ☐ prescription only

7.1	☐ non-prescription **PROPOSAL OF REGIME OF ISSUING FOR MEDICINE WHICH IS ISSUED WITH PRESCRIPTION ONLY:** ☐ Medicine is designated exclusively for treatments which can only be monitored in hospital because of its qualities and health protection (*H*) ☐ Medicine is used for treatment of diseases for which the diagnosis must be given in the hospital or institution with adequate diagnostic equipment and if taking of the medicine or monitoring of treatment may be performed also outside the hospital (*H/Rp*) ☐ Medicine is used for treatment of ambulatory patients and if its use may lead to adverse reactions, which requires prescription for the medicine from the specialist or its authorisation to another doctor, as well as special supervision during the course of treatment (*Rp/spec.*) ☐ Medicine is used only in public health-care or veterinary institutions and with legal and private persons, who perform health-care or veterinary activity (*In-patient hospital treatment*) ☐ Medicine is **used** for ambulatory treatment of illness for which it is not necessary to give diagnosis in the hospital or institution with adequate diagnostic equipment and for which taking of the medicine or monitoring of treatment may be performed also outside the hospital or health-care or veterinary institution (*Rp*)
8.	**ADVERTIZING OF MEDICINES WHICH ARE ISSUED WITHOUT PRESCRIPTION** ☐ Promotion intended for medical and veterinary workers ☐ Promotion intended for public
9.	**MANNER OF DESTROYING OF MEDICINE** ☐ Described in the pharmaceutical-biological documentation ☐ In accordance with current legislation
10.	PROPOSAL OF *EAN* CODE OF THE PRODUCT[6]: ☐☐☐☐☐☐☐☐☐☐☐☐☐

DATA ON HOLDER OF MARKETING AUTHORISATION FOR A MEDICINE	
11.	**DATA ON APPLICANT FOR MARKETING AUTHORISATION FOR A MEDICINE**

	Name of the company:	
	Short name of the company:	
	Address:	
	Applicant[7]:	
	☐ manufacturer	☐ branch office
	☐ representative[8]	other:
	Telephone: Telefax:	
	E-mail:	
12.	**PERSON RESPONSIBLE for obtaining marketing authorisation for a medicine in Montenegro**[9]	
	Name, surname, title:	
	Address of the company:	
	Telephone:	
	Telefax:	
	E-mail:	
	Legal relationship with the applicant:	
	☐ employee ☐ contract other:	
	PERSON RESPONSIBLE for pharmacovigilance in Montenegro[9]	
	Name, surname, title	
	Address of the company:	
	Telephone:	
	Telefax:	
	E-mail:	
	PERSON RESPONSIBLE for withdrawal of medicine or batch of the medicine from the market in Montenegro[9]	
	Name, surname, title	
	Address of the company:	
	Telephone:	
	Telefax:	
	E-mail:	

DATA ON MANUFACTURER OF THE MEDICINE		
13.	**DATA ON MANUFACTURER**	
	Name of the company:	
	Short name of the company:	
	Address:	
	Country:	
	Manufacturing site:	
	Number of authorisation for manufacturing of medicine[10]:	
	CONTACT PERSON OF THE MANUFACTURER	
	Name, surname, title	
	Telephone:	
	Telefax:	
	E-mail:	
14.	**MANUFACTURING SITES WHICH ARE INVOLVED IN CERTAIN PROCEDURE DURING MANUFACTURING OF THE MEDICINE[11]**	
	Name of the company:	
	Address:	
	Country:	
	Number of authorisation for manufacturing[10]:	
	PERSON RESPONSIBLE for manufacturing	
	Name, surname and title:	
	Telephone:	
	Telefax:	
	E-mail:	
	State the production phase:	
	IS INSPECTION CONTROL REGULARLY PERFORMED IN THE	

	MANUFACTURING SITES OF MANUFACTURER: **YES**[12] ☐ **NO** ☐

REMARK: make a photocopy of the page if it is necessary to state more manufacturing sites of manufacturer, which are involved in certain production procedures during the manufacturing of the medicine.

15.	**PLACE/S WHERE THE QUALITY CONTROL IS PERFORMED**	
	Name of the company:	
	Address:	
	Country:	
	PERSON RESPONSIBLE for marketing of the medicine	
	Name, surname and title:	
	Telephone:	
	Telefax:	
	E-mail:	
16.	**CONTRACTING COMPANY ENTRUSTED BY THE MANUFACTURER IN CHARGE FOR MARKETING OF BATCH OF THE MEDICINE WITH THE PART OF THE PRODUCTION PROCESS**[13]:	
	Name of the company:	
	Address:	
	Country:	
	Number of authorisation for manufacturing[10]:	
	PERSON RESPONSIBLE for manufacturing	
	Name, surname and title:	
	Telephone:	
	Telefax:	
	E-mail:	
17.	**PRODUCER OF ACTIVE SUBSTANCE**[14]	
	Name of the active substance:	

	Name of the company:	
	Address:	
	Country:	
	Telephone:	
	Telefax:	
	E-mail:	
	Submitted data on development, production and stability of active substance (DMF) or current experiences and analysis which confirm quality of active substance: YES☐ NO☐ OR Submitted European Pharmacopoeia certificate of suitability*:* YES☐ NO☐	
18.	**CONTRACTING COMPANIES WHICH PARTICIPATED IN STUDIES OF BIO-EQUIVALENCE OR IN VALIDATION OF THE PRODUCTION PROCES OF BLOOD DERIVATIVES,** if necessary [15]	
	Name of the company:	
	Address:	
	Country:	
	Telephone:	
	Telefax:	
	E-mail:	
	Role of the contracting company:	

REMARK: make a photocopy of the page if it is necessary to mention more contracting companies

COMPOSITION OF THE MEDICINE	
19.	**QUALITATIVE AND QUANTITATIVE COMPOSITION OF THE**

	MEDICINE (ACTIVE SUBSTANCES AND EXCIPIENTS)[16]		
Name of the medicine	**Quantity**	Measure unit	Reference (for example: Ph. Eur etc.)
Active substances (*INN* in language officially used in Montenegro):			
Excipients (*INN* in language officially used in Montenegro):			

Data on destruction of active substance or excipients:

20.	**LIST OF MATERIALS OF ANIMAL OR HUMAN ORIGIN WHICH WERE INCLUDED IN THE PRODUCTION PROCESS:** ☐ **THERE WERE NOT ANY** ☐ **THE FOLLOWING WERE INCLUDED** (mark appropriate boxes):

Name	AS	E	R	A-TSE	A-O	H	TSE certificate
1.	☐	☐	☐	☐	☐	☐	☐
2.	☐	☐	☐	☐	☐	☐	☐
3.	☐	☐	☐	☐	☐	☐	☐
4.	☐	☐	☐	☐	☐	☐	☐
etc.							

AS – active substance;
E - excipients;
R – reagents or cultures of medium (including those for preparation of master or work bank cells);
A-*TSE* – animal origin, susceptible to TSE risk;
A-O – animal origin, other;
H – human origin;
***TSE* certificate**[17].

21.	**IS THERE A CERTIFICATE FOR PLASMA MASTER FILE *(PMF)*:** ☐ **NO**

☐ **YES**[18], the certificate refers to:

AS	E	R
☐	☐	☐

AS – active substance;
E - excipients;
R – reagents or cultures of medium (including those for preparation of master or work bank cells);

Holder of *PMF* Certificate/Applicant for *PMF* Certificate:

No. of Certificate/Application:	
Date of submission of application:	
Date of issuance/last renewal of Certificate:	

22.	**DOES THE MEDICINE CONTAIN GMO (GENETICALLY MODIFIED ORGANISMS):** ☐ **NO** ☐ **YES** ☐ submitted evidence from competent institutions that the product is in compliance with laws on environmental protection[19] ☐ no evidence was submitted from competent institutions that the product is in compliance with laws on environmental protection
23.	**DATA ON MAXIMUM RESIDUE LIMIT (*MRL*) – FOR VETERINARY MEDICINES FOR ANIMALS WHICH ARE USED FOR HUMAN CONSUMPTION:**
24.	**DATA ON WAITING PERIOD – FOR VETERINARY MEDICINES FOR ANIMALS WHICH ARE USED FOR HUMAN CONSUMPTION:**

25.	**DATA ON PREMIX – FOR MEDICINES TO BE USED IN VETERINARY MEDICINE:**
26.	**OTHER RELEVANT DATA:**

DATA ON DISTRIBUTER		
27.	**PLANNED DISTRIBUTION OF A MEDICINE**	
	Manufacturer in Montenegro:	
	Manufacturer in EU	
	Manufacturer outside EU:	
	PERSON RESPONSIBLE for marketing of medicine	
	Name, surname and title	
	Telephone:	
	Telefax:	
	E-mail:	
	IMPORTER FOR MONTENEGRO	
	Name of the company:	
	Address of the company:	
	DISTRIBUTER IN MONTENEGRO	
	Name of the company:	
	Address of the company:	
	RESPONSIBLE PERSON OF DISTRIBUTER	
	Name, surname and title	

	Telephone:	
	Telefax:	
	E-mail:	

REMARK: make a photocopy of the page if it is necessary to name more distributers

28. MARKETING AUTHORISATIONS FOR MEDICINE IN OTHER COUNTRIES	
country: **number and date of issuance of authorisation:** **name of medicine:**	
country: **number and date of issuance of authorisation:** **name of medicine:**	
country: **number and date of issuance of authorisation:** **name of medicine:**	
country: **number and date of issuance of authorisation:** **name of medicine:**	
country: **number and date of issuance of authorisation:** **name of medicine:**	
In the registration procedure:	**country:** date of application: **country:** date of application:
Application requested:	country: date of application: reason:
Applicant withdrew application before issuance of marketing authorisation for a medicine:	**country:** date of withdrawal: name of medicine: reason for withdrawal:
Holder of marketing authorisation for a medicine withdrew the medicine from the market:	**country:** date of withdrawal: name of medicine: reason for withdrawal:
Competent institution of the country which withdrew the medicine from the market:	**country:** date of withdrawal: name of medicine: reason for withdrawal:

REMARK: make a photocopy of the page if necessary

DOCUMENTATION	
29.	**STRUCTURE OF DOCUMENTATION:** ☐ Common Technical Document (*CTD*) ☐ European (EU) file
29.1	**EUROPEAN (EU) FILE:** **IA ☐ ADMINISTRATIVE DATA** part _____ page _____ to _____ **IB ☐ SUMMARY OF CHARACTERISTICS OF MEDICINE** part _____ page _____ to _____ **IC ☐ EXPERT REPORTS:** ☐ For pharmaceutical-chemical-biological documentation part _____ page _____ to _____ ☐ For pharmacological-toxicological documentation ☐ For testing of the safety and residue for veterinary medicine ☐ For testing of the safety for veterinary immunobiological medicine ☐ For clinical documentation ☐ For pre-clinical and clinical documentation for veterinary medicine ☐ For examination of efficiency for veterinary immunobiological medicine part _____ page _____ to _____ ☐ **INSTRUCTION FOR PATIENT** ☐ **PROPOSAL OF PACKAGING OF MEDICINE** **II ☐ PHARMACEUTICAL-CHEMICAL-BIOLOGICAL DOCUMENTATION** part _____ page _____ to _____ **III ☐ PHARMACOLOGICAL-TOXICOLOGICAL DOCUMENTATION** ☐ **SAFETY AND EXAMINATION OF RESIDUE** for veterinary medicine ☐ **TESTING OF SAFETY** for veterinary and immunological

	medicine part _____ page _____ to _____ **IV ☐ CLINICAL DOCUMENTATION** ☐ **DOCUMENTATION ON PRE-CLINICAL AND CLINICAL TRIALS** for veterinary medicine ☐ **EXAMINATION OF EFFICIENCY** for veterinary and immunobiological medicine part _____ page _____ to _____

29.2 COMMON TECHNICAL DOCUMENT:

☐ Module 1
part _____ page _____ to _____

☐ Module 2
part _____ page _____ to _____

☐ Module 3
part _____ page _____ to _____

☐ Module 4
part _____ page _____ to _____

☐ Module 5
part _____ page _____ to _____

30. LIST OF ENCLOSED DOCUMENTS:

30.1 ☐ Proof that all the stipulated fees are paid

30.2 ☐ Consent of the holder of the marketing authorisation for original medicine to refer to data on pharmacological-toxicological examination and clinical trial of the medicine from his/her documentation

30.3 ☐ Registration certificate for legal or natural person in Montenegro

30.4 ☐ Agreement on business and technical cooperation

30.5 ☐ *Curriculum Vitae* of responsible person and Authorisation for communication with the Agency

30.6 ☐ Authorisations for manufacturing and confirmation in which more than one place for marketing of batch of medicine are suggested

30.7 ☐ Scheme of connections between various manufacturing sites included in different production procedures in the production of one medicine

30.8 ☐ *GMP* Certificate from competent institution and following data:

- Date of last inspection;
- name of competent body which performed inspection;
- type of inspection and report of inspector.

30.9 Authorised copy of the authorisation for manufacturing of the contracting company entrusted by the manufacturer in charge for marketing of medicine in Montenegro with the part of the production process

30.10 Copy of *DMF* active substance or current experience and analysis which confirm adequate quality of active substance, copy of written consent of producer of active substance regarding every change in *DMF*, and copy of European Pharmacopoeia certificate of suitability.

30.11 *TSE* certificate (i)

30.12 *PMF* certificate

30.13 Written consent of competent institution which refers to releasing of GMO into environment

I hereby declare that all data relevant for assessment of quality, safety and efficiency of medicine can be found in the enclosed documentation.	
Name, surname and title of responsible person	
_____	_____
Date	Signature of responsible person

[1] Form should be filled in for each pharmaceutical form and strength and packaging
[2] To submit the document 30.2
[3] Indications are to be stated with nomenclature and code according to International Classification of Diseases (ICD 10)
[4] For medicinal products for veterinary use it is necessary to state target kinds of animals or categories
[5] To include description of quality of packaging material and submit conceptual design or samples of packaging
[6] To state 13 or 8 numbers in accordance with the Rulebook on Labelling of Medicines
[7] To submit the document 30.3
[8] To submit the document 30.4
[9] To submit the document 30.5, if the person responsible for marketing of medicine is also responsible person for pharmacovigilance and procure of withdrawal of medicine or batch of medicine from the market, the same data should be repeated.
[10] To submit documents 30.6
[11] To submit documents 30.7
[12] To submit documents 30.8
[13] To submit documents 30.9

[14] **To submit documents 30.10**
[15] **To state separately for each contracting company**
[16] **To state pharmaceutical form to which the data refers: for example to 1 capsule**
[17] **If exists, submit document 30.11**
[18] **To submit document 20.12**
[19] **To submit document 30.13**

ANNEX 2

STRUCTURE OF THE COMMON TECHNICAL DOCUMENT (CTD file)

CTD file shall consist of parts which encompass:

Part I: CTD file with standard applications

Part II: CTD file with specific regulatory applications

Part III: CTD file with specific applications considering the origin of active substance

Part IV: CTD file with specific applications for medicines which are used in advanced therapies

Part I: CTD file with standard applications shall consist of 5 parts i.e. modules.

Module 1 – Contains administrative and regional data:

1.1. Detailed overview of contents of documentation in the form of CTD file

1.2. Application form (completed form from Annex 1 of this Rulebook is to be submitted again)

1.3. Proposal of the summary of characteristics of the medicine, proposal of instruction for patient and proposal of outer and immediate packaging, namely:

1.3.1. Proposal of summary of characteristics of medicine

1.3.2. Proposal of instruction for patient

1.3.3. Proposal of outer and immediate packaging

1.4. Data on experiments whose appraisal of documents on quality, safety and efficiency has been submitted by the applicant (biographical and bibliographical data as well as connection with future holder of authorisation, signature of expert)

1.5. Special requests for bibliographical documentation or shortened documentation:

1.5.1. Data necessary for request for bibliographical data

1.5.2. Data necessary for request with shortened documentation

1.6. Environmental risk assessment

Annex 1: Environmental risk assessment

Annex 2: Evaluation of therapeutic benefit of medicines which are used for treatment of rare diseases (orphan disease)

1.8. Detailed description of the pharmacovigilance system

1.9. Risk management plan

Proposal of summary of characteristics of medicine and proposal of instruction for patient referred to in the item 1.3.1. and 1.3.2. of the Module 1 shall be submitted in Montenegrin language.

Proposal of instruction for patient, in certain cases, may submitted in Serbian, Croatian or Bosnian language for approval of the Agency.

Beside the proposal of the summary of characteristics of the medicine and instruction for patient in Montenegrin language it is necessary to submit the last approved version of the summary of characteristics of the medicine and instruction for patient approved by:

1. EMEA, if the medicine has received marketing authorisation for European Union according to the centralised procedure;

2. Reference Member states, if the medicine has received marketing authorisation for European Union according to the decentralised procedure or mutual recognition procedure;

3. Competent Agency, if the medicine has received marketing authorisation according to the national procedure;

Documents referred to in the item 1, 2 and 3 shall be submitted in English language.

Except in English language, documents referred to in the item 3 may be submitted, in certain cases also in Serbian, Croatian or Bosnian language.

Proposal of summary of characteristics of the medicine and instruction for patient in Montenegrin language must fully comply i.e. professionally and linguistically authorised

translation of relevant documents referred to in the item 1 or 2 or 3, which shall be confirmed by the appropriate statement of the applicant.

Module 2 - Concise expert reports and overview of Module 3, 4 and 5, shall contain:

2.1. Detailed overview of contents of Module 2
2.2. Introduction
2.3. Total summary of quality of medicine
2.4. Overview of documentation on pre-clinical examinations
2.5. Overview of documents on clinical trials
2.6. Summary of documentation on pre-clinical examination
- 2.6.1. Textual form of summary of pharmacological data
- 2.6.2. Table form of pharmacological data
- 2.6.3. Textual form of summary of pharmacokinetic data
- 2.6.4. Table form of pharmacokinetic data
- 2.6.5. Textual form of summary of toxicological data
- 2.6.6. Table form of toxicological data

2.7. Summary of documentation on clinical trial
- 2.7.1. Summary on biopharmaceutical medicines and appropriate analytic methods
- 2.7.2. Summary of examination from classic pharmacology
- 2.7.3. Summary on clinical efficiency
- 2.7.4. Summary on clinical safety
- 2.7.5. Short overview of individual examinations

Module 3 – Data on quality shall contain:

3.1. Detailed overview of contents of Module 3
3.2. Data on active substance and on finished medicine
- 3.2.C Active substance
  - 3.2.C.1. General data
    - 3.2.C.1.1. Nomenclature
    - 3.2.C.1.2. Structure
    - 3.2.C.1.3. General qualities
  - 3.2.C.2. Manufacturing
    - 3.2.C.2.1. Manufacturing sites
    - 3.2.C.2.2. Description of production procedure and process control
    - 3.2.C.2.3. Control of all starting substances
    - 3.2.C.2.4. Control of critical phases and intermediates
    - 3.2.C.2.5. Validation of production process and/or evaluation
    - 3.2.C.2.6. Development of production process
  - 3.2.C.3. Characterisation
    - 3.2.C.3.1. Explanation of structure and other qualities
    - 3.2.C.3.2. Impurities
  - 3.2.C.4. Control of active substance
    - 3.2.C.4.1. Specifications
    - 3.2.C.4.2. Analytical methods
    - 3.2.C.4.3. Validation of analytical methods
    - 3.2.C.4.4. Analysis of the batch
    - 3.2.C.4.5. Confirmation of specification
  - 3.2.C.5. Reference standards and materials
  - 3.2.C.6. System of closing of containers
  - 3.2.C.7. Stability
- 3.2.P Final product/medicine
  - 3.2.R.1. Description and composition of the medicine
  - 3.2.R.2. Development of the medicine
  - 3.2.R.3. Manufacturing
    - 3.2.R.3.1. Manufacturer/s
    - 3.2.P.3.2. Manufacturing formula
    - 3.2.P.3.3. Description of production process and process control
    - 3.2.P.3.4. Control of critical phase and intermediates

3.2.P.3.5. Validation of the production process and/or evaluation
3.2.P.4. Control of excipients
3.2.P.4.1. Specifications
3.2.P.4.2. Analytical methods
3.2.P.4.3. Validation of analytical methods
3.2.P.4.4. Confirmation of specification
3.2.P.4.5. Excipient of human or animal origin
3.2.P.4.6. New excipients
3.2.P.5. Control of finished product/medicine
3.2.P.5.1. Specifications
3.2.P.5.2. Analytical methods
3.2.P.5.3. Validation of analytical methods
3.2.P.5.4. Analyses of batches
3.2.P.5.5. Characterisation of impurities
3.2.P.5.6. Confirmation of specifications
3.2.P.6. Reference standards and materials
3.2.P.7. System for closing of containers
3.2.P.8. Stability
3.2.A Annexes
3.2.A.1. Premises and equipment
3.2.A.2. Evaluation of safety of medicine regarding the side products (metabolites, degradation products)
3.2.A.3. New excipients
3.2.P Regional information
3.3. Reference to the literature

Module 4 – Pre-clinical examination of the medicine include:
4.1. More detailed overview of the contents of the Module 4
4.2. Reports of examinations
4.2.1. Pharmacology
4.2.1.1. Primary pharmacodynamics
4.2.1.2. Secondary pharmacodynamics
4.2.1.3. Pharmacology of the safety of medicine
4.2.1.4. Pharmacodynamic interactions
4.2.2. Pharmacokinetics
4.2.2.1. Validation of analytical method
4.2.2.2. Resorption
4.2.2.3. Distribution
4.2.2.4. Metabolism
4.2.2.5. Discharging
4.2.2.6. Pharmacokinetic interactions (non-clinical)
4.2.2.7. Other pharmacokinetical examinations
4.2.3. Toxicology
4.2.3.1. Toxicity after the application of one dose of medicine
4.2.3.2. Toxicity after the application of repeated doses of medicine
4.2.3.3. Mutagenesis
4.2.3.4. Cancerousness
4.2.3.5. Reproductive toxicity
4.2.3.6. Local tolerance
4.2.3.7. Other toxicological examinations
4.3. Reference to the literature

Module 5 – Clinical trials of the medicine shall contain:
5.1. Detailed overview of contents of the Module 5
5.2. Table overview of all clinical trials
5.3. Reports on clinical trial
5.3.1. Reports on examinations of bio-availability/bio-equivalence
5.3.2. Reports on examinations of pharmacokinetics of human biomaterial
5.3.3. Reports on pharmacokinetic testing on humans
5.3.4. Reports on pharmacodynamic testing on humans

5.3.5. Reports on testing of efficiency and safety
5.3.6. Reports on post-marketing experiences
5.3.7. Reports on individual cases and test lists of patients if they are submitted
5.4. Reference to the literature

Part II: CTD file with specific regulatory requests shall encompass:

1. Medicines whose active substance/s have the known safety and acceptable efficiency and is being used in the form of the medicine for at least 10 years and for which there are enough bibliographical data and sufficient level of convergence of scientific statements.
2. Essentially similar medicines for which it is necessary to prove a statement on essential similarity, assess impurities and degradable products and their influence on safety and efficiency of finished medicine. It is necessary to assess bio-equivalent studies or explain the reasons why they have not been performed according to scientific-technical guidelines. Each statement which is not shown in the documentation of the reference medicine or in its summary of characteristics, must be supported by pre-clinical or clinical studies or bibliographic data.
3. For essentially similar medicine which require additional data for special situations (for example in case of different salts, esters of the same active substance) it is necessary to have evidence that it does not affect the safety and efficiency profile or the essential similarity.
4. It is necessary to compare biologically similar medicines from case to case taking into account the level of difference because of which the medicines cannot be listed as essentially similar.
5. Fixed combinations of medicines shall be documented as new substance except for data for each active substance separately, specially of they are already in the medicine which received marketing authorisation.
6. Medicines with incomplete documentation, which are used in special situations (for example necessary medicines for rare diseases, for difficult diseases, for treatment of therapeutic groups of patients for which there are ethical problems for approval of clinical studies etc.).
7. Medicines containing combined documentation in the modules 4 and 5. Parts of documentation which were not covered by own data, shall be covered by bibliographical data and completed in the overall documentation.

Part III: CTD file with specific requests regarding the origin of active substance shall contain:

1. Biological medicines: medicines from blood or plasma must have data on the source of plasma, manner of collecting and testing. Vaccines must have data on antigens of the vaccine, type of vaccine, way of manufacturing, consistence of batches and existing certificates.
2. Radio-pharmaceutical medicines: active substance of radio-pharmaceutical medicines is the part of formulation binding or carrying radionuclide.
3. Homeopathic remedies: those are medicine which have the concentration of active substance 1:100 when compared to concentrations in allopathic treatment and 1:10000 when compared to parent concentration of active substance.
4. Herbal medicines: those are medicines whose active substance is of herbal origin. When possible, documentation should be prepared as with the standard CTD file.
5. Orphan medicines: Medicine shall obtain status of orphan medicine based on classification confirmed by the European Medicines Agency (EMEA) for medicines which are used for treatment of diseases with incidence less than 5/10000.

Part IV: CTD file with specific requests for medicines which are used in advanced therapies (for example: gene therapy). Those are medicines:

1. which are made based on application of allogen or xenogen cells by action of vector of viral or non-virus source. The cells genetically modified by the vector represent an active substance.
2. which are used for gene treatment with autologous human cells obtained from individual patient in which the active substance is the prepared vector which shall be transferred into autogenous cells in order to get the final product (finished medicine).

3. which are used in the form of prepared vectors with inserted genetic material (for diagnostic or therapeutic purposes). Active substance is prepared vector with inserted genetic material.

4. which are products of tissue engineering

Definition and special conditions for this type of medicines have to be in line with the Regulation 1394/07/EC

Products of tissue engineering are:

- medicines obtained in a way which allows that prophylactic, diagnostic or therapeutical gene is transferred through the transfer system into cells and to allow for its expression *in vivo*
- medicines produced in the way which allows that autologous, allogen or xenogen cells change in such manner, that they can be used for achieving prophylactic, diagnostic or therapeutic effect

Medicines which belong to tissue engineering:

- contain or are composed of cells or tissues produced by tissue engineering and
- have qualities with which they can repair, replace or regenerate human tissue

Cells or tissues produced by tissue engineering, must meet at least one of the following conditions:

- cells or tissues are subject of substantial manipulation, which changed their biological characteristics, physiological functions or characteristics important for regeneration, replacing or repairing of human tissue
- cells or tissues are not meant to homologous use (the same essential function or functions in receiver and donor)

Substantial manipulations, for the purpose of this Rulebook, are not:

cutting, grinding, centrifuging, moulding, sterilisation, radiation, separation, concentrating, cleaning, filtering, lyophilisation, freezing, vitrification, storing by freezing, soaking (into antimicrobial solutions)

Special conditions for products of tissue engineering:

- cells and tissues are obtained, processed and kept in accordance with the Directive 2004/23/EC
- provisions of regulations and guidelines related to Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) shall be amended with special requirements
- provisions of regulations and guidelines on medical devices shall refer also to medical devices in combined product
- provisions of regulations and guidelines on tissue engineering shall include also description of material and other qualities of the product as well as the description of the production plan in accordance with the Directive 2001/83/EC
- provisions of regulations and guidelines shall be amended with regard to the technical requirements for tissue engineering
- beside existing ones, there are also the special requirements (description of the product, traceability, statement on cells if they are in the product, their description and stating of the origin...)

ANNEX 3

STRUCTURE OF EUROPEAN (EU) FILE

EU file shall contain four (4) parts

a) EU file for medicinal products for human use shall contain:

I Part of the file

IA Administrative data:

IAa completed form of application which is in the Annex 1 of this Rulebook;

IAb proof that the applicant meets all conditions stipulated by the law or referring to data already submitted to the Agency;

IAc GMP certificate/s (good manufacturing practice) for manufacturing site/s;

IAd list of countries in which the medicine received authorisation or in which the application for marketing authorisation for the medicine was rejected or the authorisation was revoked or in which the validity of the licence has terminated, as well as names of countries in which the medicine received the first marketing authorisation;

IAe Certificates of Pharmaceutical Product (for medicine), Free Sale Certificate (on sale of medicine). In case when medicine is produced by the manufacturer who has more manufacturing sites in the same or in different countries, scheme of their connection shall be submitted to the Agency for proper interpretation of the term "country of origin";

IAf data on given samples of medicine and standards;

IAg PSUR (Periodic Safety Update Report of medicine) if the medicine has already been on the market in other countries;

IAh Other data upon request of the Agency, which are necessary for control of quality, safety and efficiency of the medicine i.e. for health protection.

IB Proposal of SmPC (Summary of Product Characteristics), instruction for patient and proposal of packaging of medicine

IB 1. Proposal of SmPC.

IB 2. Proposal of instruction for patient or user.

IB 3. Proposal of packaging of medicine.

IC Reports of experts on documentation regarding quality, safety and efficiency of the medicine, which are also integral part of the documentation. Basic data on experts are also submitted (biographical, bibliographical) and their connection with the applicant for authorisation. Reports of experts shall include:

- summarised profile of the medicine: type of application, chemical and pharmacokinetical qualities of the medicine, indications, warnings, pharmacovigilance data, etc.;
- table overview of data;
- critical review of contents of certain parts of documentation and harmonisation with the summary of the characteristics of the medicine;
- summary of expert report in the form of text or tables and final expert opinion;
- amendments to reports if there are any, signature of expert.

II part of the file - pharmaceutical-chemical-biological documentation:

IIA data on composition of the medicine (qualitative and quantitative composition, data on packaging and development of the medicine);

IIB description of the production process (production formula, production process, process control, validation of the production process);

IIC control of starting substances and materials for packaging (active substance/s described in pharmacopeia, with specification and routine tests as well as the material for packaging with specification and routine tests)

IICa: TSE certificate and special measures of prevention of Transmissible spongiform encephalopaties;

IID control methods for intermediate products (specifications and routine tests, examination methods, scientific data, validation and analytical methods);

IIE control methods for finished medicine;

IIF stability studies (for active substance and finished medicine);

IIG bio-equivalence / bio-availability if necessary;

IIH ecotoxicity or environmental risk in case the medicine contains genetically modified organisms;

IIQ other data on medicine;

IIR virusologic documentation.

III part of the file – pharmacological – toxicological documentation:

IIIA toxicity after application of one or more repeated doses;

IIIB influence on reproductive functions (fertility and general reproductive characteristics);

IIIC embryo-fetal and perinatal toxicity;

IIID mutagenicity in vivo and in vitro;

IIIE cancerousness;

IIIF pharmacodynamics;

IIIG pharmacokinetics;

IIIH local tolerance, if necessary;

IIIQ other data on medicine;

IIIR ecotoxicity and environmental risk.

IV part of the file – clinical documentation:

IVA clinical pharmacology

- pharmacodynamic data (overview of examinations, detailed protocol of trials, results which encompass characteristics of examined population, results of testing of efficiency and safety as well as the analysis of those results, conclusions and reference to bibliographical data);
- pharmacokinetical data (overview of examinations, detailed protocol of trials, results and conclusions of testing as well as the reference to bibliographical data).

IVB clinical experiences (results of published and unpublished, finished or unfinished clinical trials, post-marketing experiences if any, pharmacovigilance date;

IVI bibliographical data which refer to the medicine for which authorisation is required or to medicine with the same active substance with data on differences and connection of medicine from literature data and medicine for which authorisation is required;

IVQ other data on medicine.

b) EУ file for medicinal products for veterinary use shall contain:

IA Administrative data:

IAa Completed application form which is in the Annex 1 of this Rulebook;

IAb Proofs that the applicant meets conditions stipulated by the law or reference to data which have already been submitted to the Agency;

IAc GMP certificate/s (Good Manufacturing Practice) for manufacturing site/s;

IAd List of countries in which the medicine for which authorisation is required has already received marketing authorisation;

IAe Certificates of Pharmaceutical Product (for medicine), Free Sale Certificate (on sale of medicine);

IAf Data on given samples of medicine and standards;

IAg PSUR (Periodic Safety Update Report of medicine) if the medicine has already been on the market in other countries;

IAh Other data upon request of the Agency, which are necessary for control of quality control, safety and efficiency of the medicine i.e. for health protection

IB Proposal of SmPC (Summary of Product Characteristics), instruction for patient and proposal of packaging of medicine

IB 1. Proposal of SmPC;

IB 2. Proposal of instruction for user;

IB 3. Proposal of packaging of the medicine;

IC Reports of experts on documentation regarding quality, safety and efficiency of the medicine, which are also integral part of the documentation. Basic data on experts are also submitted (biographical, bibliographical) and their connection with the applicant for authorisation.

II part of the file - pharmaceutical-chemical-biological documentation:

IIA data on composition of the medicine (qualitative and quantitative composition, data on packaging and development of the medicine);

IIB description of the production process (production formula, production process, process control, validation of the production process);

IIC control of starting substances and materials for packaging (active substance/s described or not described in pharmacopeia, with specification and routine tests, excipients described or not described in pharmacopoeia with specifications and routine tests as well as the material for packaging with specification and routine tests)

IICa: TSE certificate and special measures of prevention of Transmissible spongiform encephalopaties;

IID control methods for intermediate products (specifications and routine tests, examination methods, scientific data, validation and analytical methods);

IIE control methods for finished medicine;

IIF stability studies (for active substance and finished medicine);

IIG bio-equivalence / bio-availability if necessary;

IIH ecotoxicity or environmental risk in case the medicine contains genetically modified organisms;

IIQ other data on medicine.

III part of the file – data on examination of safety of residue

III A – data on examination of safety:

- introduction;
- pharmacological data (pharmacodynamics and pharmacokinetics);
- toxicological data (toxicity after one dose, toxicity after repeated doses, tolerance with target kinds of animals, reproductive toxicity and teratogenicity, mutagenicity, cancerousness, exceptions for example local tolerance);
- examinations of other effects (special testing of immunotoxicity, neurotoxicity and examination of endocrine functions, observations on humans, microbiological testing, examinations of metabolites of impurities and other substances);
- examinations of safety for users or medical worker or animal owner with proposal for risk reduction;
- ecotoxicity.

III B – data on examination of residue
- introduction;
- metabolism of residue;
- pharmacokinetical parameters of residue, disposal, MRL (Maximal Residue Limit) and waiting period;
- routine analytical methods for discovering of residue.

IV part of the file – documentation on pre-clinical and clinical trials
IV A Pre-clinical documentation
- pharmacological data on medicine which encompass:
- pharmacodynamical data and
. pharmacokinetical data (absorption, distribution, metabolism and discharging);
- tolerance with target kinds of animals and
- resistance.

IV B Clinical documentation
- general principles of performed clinical trials;
- documentation on performed trials.

c) EU file for immunological veterinary medicines shall contain:
IA Administrative data:
IAa completed form of application which is in the Annex 1 of this Rulebook;
IAb proof that the applicant meets all conditions stipulated by the law or referring to data already submitted to the Agency;
IAc GMP certificate/s (good manufacturing practice) for manufacturing site/s;
IAd list of countries in which the medicine for which authorisation is required has already received marketing authorisation.
IAe IAe Certificates of Pharmaceutical Product (for medicine), Free Sale Certificate (on sale of medicine);
IAf data on given samples of medicine;
IAg PSUR (Periodic Safety Update Report of medicine) if the medicine has already been on the market in other countries;
IAh Other data upon request of the Agency, which are necessary for control of quality, safety and efficiency of the medicine i.e. for health protection.
IB Proposal of SmPC (Summary of Product Characteristics), instruction for patient and proposal of packaging of medicine
IB 1. Proposal of SmPC.
IB 2. Proposal of instruction for user;
IB 3. Proposal of packaging of medicine.
IC Reports of experts on documentation regarding quality, safety and efficiency of the medicine which are also integral part of documentation. Basic data on experts are also submitted.

II part of the file - pharmaceutical-chemical-biological documentation:
IIA data on composition of medicine (qualitative and quantitative composition, data on packaging and development of medicine);
IIB description of the production process (production formula, production process, process control, validation of the production process);
IIC control of starting substances and materials for packaging (active substance/s described or not described in pharmacopoeia, with specification and routine tests, excipients

described or not described in pharmacopoeia with specifications and routine tests as well as the material for packaging with specification and routine tests)

IICa: TSE certificate and special measures of prevention of Transmissible spongiform encephalopaties;

IID control methods for intermediate products (specifications and routine tests, examination methods, scientific data, validation and analytical methods);

IIE control methods for finished medicine;

IIF stability studies (for active substance and finished medicine);

IIG bio-equivalence / bio-availability if necessary;

IIH ecotoxicity or environmental risk in case the medicine contains genetically modified organisms;

IIQ other data on medicine.

III part of the file for immunological veterinary medicines shall contain:

- introduction;
- general requirements for safety testing;
- laboratory testing (safety after one dose and after repeated doses, safety after overdosing, examination of reproductive functions, immunological functions, special requests for live vaccines, testing of residue, interactions);
- examination on the field;
- ecotoxicity.

IV part of the file for immunobiological veterinary medicines shall contain:

- introduction;
- general requirements for efficiency testing;
- laboratory testing;
- examination on the field;
- general conclusions;
- reference to the bibliographical data.

ANNEX 4

I STRUCTURE AND CONTENTS OF THE SUMMARY OF BASIC CHARACTERISTICS OF MEDICINAL PRODUCT FOR HUMAN USE

1. Name of the medicine:

Name, strength and pharmaceutical form

2. Qualitative and quantitative composition

Data on active substance shall be stated as well as the data on international non-protected name of the medicine (INN) or generic name and excipients.

3. Pharmaceutical form

4. Clinical details

4.1. therapeutic indications;

4.2. dosing and way of use;

4.3. contraindications;

4.4. special warnings and safety measures;

4.5. clinically important interactions;

4.6. use during pregnancy or breast-feeding;

4.7. influence on psychophysical abilities or driving ability or ability to work with technical equipment;

4.8. Adverse reactions to the medicine;

4.9. Overdosing and measures to be taken.

5. Pharmacological characteristics

5.1. pharmacodynamic characteristics;

5.2. pharmacokinetic characteristics;

5.3. Pre-clinical data on safety;
5.4. Dosimetric data in the case of radio-pharmaceutical medicines.

6. Pharmaceutical details
6.1. list of excipients;
6.2. incompabilities;
6.3. shelf life;
6.4. special warnings for storing of medicine;
6.5. type and contents of the container;
6.6. instruction for use/handling for patient or medical worker;
6.7. proposed/approved regime of issuing of a medicine (Rp, HRp);
6.8. special information for radio-pharmaceutical medications.

7. Holder of authorisation (name, address, contact details)

8. Number of authorisation

9. Date of first marketing authorisation for a medicine

10. Date of last revision of text of summary of basic characteristics of a medicine

II STRUCTURE AND CONTENTS OF SUMMARY OF BASIC CHARACTERISTICS OF A MEDICINAL PRODUCT FOR VETERINARY USE

1. Name of the medicine:
Name, strength and pharmaceutical form

2. Qualitative and quantitative composition
Data on active substance shall be stated as well as the data on international non-protected name of the medicine (INN) or generic name. Excipients shall be stated if that is necessary for safety of giving medicine.

3. Pharmaceutical form

4. Pharmacological and pharmacokinetical characteristics
4.1. pharmacodynamical characteristics;
4.2. pharmacokinetical characteristics;
4.3. environmental influence.

5. Clinical details
5.1. target kinds of animal;
5.2. therapeutic indications;
5.3. contraindications;
5.4. adverse reactions;
5.5. special warnings and safety measures;
5.6. use during pregnancy or lactation;
5.7. interactions;
5.8. dosing and way of use;
5.9. overdosing and measures to be taken;
5.10. special warnings;
5.11. waiting period;
5.12. special safety measures for person who is giving the medicine to the animal.
5. Pharmacological characteristics
5.1. pharmacodynamical characteristics;
5.2. pharmacokinetical characteristics;
5.3. pre-clinical data on safety of the medicine;
5.4. Dosimetric data in the case of radio-pharmaceutical medicines.

6. Pharmaceutical details

6.1. incompatibilities;
6.2. shelf life;
6.3. special warnings for storing of medicine;
6.4. type and contents of the container;
6.5. special warnings for destruction of unused medicine or waste;
6.6. instruction for use/handling for person who is giving the medicine to the animal;
6.7. proposed/approved regime of issuing of a medicine (Rp, Rp/stac).

7. Holder of authorisation (name, address, contact details)

8. Number of authorisation

9. Date of first marketing authorisation for a medicine

10. Date of last revision of text of summary of basic characteristics of a medicine

ANNEX 5

LIST OF VARIATIONS OF TYPE IA AND IB WITH TECHNICAL REQUIREMENTS FOR RESPECTIVE VARIATIONS

Variations type IA and IB are smaller variations and refer to the following variations with condition to fulfil technical requirements for respective variations:

1. Change of name and/or address of the holder of authorisation if the holder of authorisation shall remain the same legal entity (IA).

2. Change of the name of the medicine not assuming the possibility of confusion with names of medicines which already have authorisation under protected or non-protected name (IB).

3. Change of the name of active substance, if the active substance remains the same (IA).

4. Change of the name and/or address of manufacturer of active substance if European Pharmacopeia Certificate of Suitability has not been submitted, national or other recognised pharmacopeia and if the manufacturing site remains the same (IA).

5. Change of the name and/or address of the manufacturer of finished medicine, if the manufacturing site remains the same (IA)

6. Change of ATC code or ATC vet. code after granting or change by WHO (IA).

7. Change or additional manufacturing site for part of procedures or for all procedures of production of finished medicine:

a) if the change refers to the manufacturing site of outer packaging for all pharmaceutical forms and under additional conditions which are stated under items 1) and 2) and apply to item 7 (IA);

b) if the change refers to the manufacturing site of immediate packaging:

I of solid pharmaceutical forms and under additional conditions stated under 1), 2), 3) and 5) which apply to item 7 (IA);

II semi-solid or liquid pharmaceutical forms and under additional conditions stated under 1), 2), 3) и 5) which apply to item 7 (IB) and

III liquid pharmaceutical forms and under additional conditions stated under 1), 2), 3), 4) and 5), which apply to item 7 (IB);

c) if the change refers to the manufacturing site in which other procedures are performed, except for marketing of medicine and under additional conditions stated under 1), 2), 4) and 5) which apply to 7 (IB).

Additional conditions which apply to item seven (7) are:

1) satisfying inspection report based on the request from GMP;
2) manufacturing site has authorisation for production of the stated pharmaceutical form;
3) it is not a sterile product;

4) there is a validation scheme in accordance with the existing protocol which has been checked on at least three production batches and

5) it is not a biological medicine.

8. Change of conditions for marketing if batch of medicine and quality controls of finished medicine:

a) if it is the change or additional place of marketing of batch of medicine under additional conditions stated under 2), 3), or 4) which apply to item 8 (IA);

b) if it is the change of manufacturer or of additional manufacturer responsible for marketing of batch of medicine:

I if the change does not involve control of the batch of medicine under the additional conditions stated under 1), 2), which apply to item 8 (IA)

II if the change involves control of batch and under additional conditions stated under 1), 2), 3) and 4) which apply under 8 (IA)

Additional conditions which apply to item 8 are:

1) manufacturer responsible for marketing of the batch of medicine, shall be situated at the territory of Montenegro;

2) manufacturing site has the appropriate authorisation for manufacturing;

3) product is not a biological medicine;

4) transfer from the old to the new manufacturing site or place of laboratory testing has been successfully solved.

9. Cancellation of any manufacturing site, including the place of manufacturing of active substance, semi-finished products or finished products, place of packaging, manufacturer responsible for marketing of the batch of medicine, place where the control of the batch of medicine is performed (IA)

10. Smaller changes in the production process of active substance (IB) under the following conditions:

1) there are no changes in qualitative or quantitative profile of impurities or in physicochemical characteristics of the medicine;

2) active substance is not biological substance;

3) way of synthesis remains the same or intermediates remain the same. In the case of herbal medicines, geographical origin, production of herbal substance and way of manufacturing remain the same.

11. Change of the size of the scale batch in the production of active substance or intermediates:

a) if the size of the scale batch is increased 10 times when compared to the size of the scale batch which has been approved by obtaining marketing authorisation and under the additional conditions stated under 1), 2), 3) and 4) which apply to item 11 (IA);

b) if the size of the scale batch has been reduced and under additional conditions 1), 2), 3), 4) and 5) which apply to item 11 (IA);

c) if the size of the scale batch has been increased or reduced for more than 10 times when compared to the size of the scale batch which was approved by obtaining of the marketing authorisation for a medicine and under the additional conditions 1), 2), 3) and 4) which apply to item 11 (IB).

Additional conditions apply to item 11 are:

1) changes of the production procedure which are result of changes of equipment which caused the change of the scale batch size;

2) there are results of examination of at least two scale batches according to specifications for proposed size of the scale batch;

3) active substance is not a biological substance;

4) change does not affect the possibility of repeating of the process;

5) The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

12. Change of specification of active substance, starting substances, or reagents which are used in the process of production of active substance:

a) if it is the case of tightening of the specification limits and under additional conditions 1), 2) and 3), which apply to 12 (IA); and under additional conditions 2) and 3) which apply to this item (IB);

b) if it is the case of adding of new parameter of testing to the specification:

I active substances and under additional conditions 2), 4) and 5) which apply to item 12 (IB)

II starting substances, intermediates or reagents which are used in the procedure of production of active substance under the additional conditions 2) and 4), which apply to item 12 (IB)

Additional conditions which apply to item 12 are:

1) change is not a result of previously determined specification limits approved in the procedure of obtaining marketing authorisation for a medicine or later in the procedure of approval of variations type II;

2) change is not result of unexpected events arising during manufacture;

3) all changes are within the currently approved limits of specifications;

4) any new test method does not concern a novel non-standard technique or a standard technique used in a novel way;

5) active substance is not biological substance.

13. Change of the procedure of testing of the active substance or starting substances, intermediates or reagents which are used in the production process of active substance:

a) if it is a case of smaller changes of currently approved testings and under additional conditions 1), 2), 3) and 5), which apply to item 13 (IA);

b) changes of the testing procedures which include changes in the very procedure of testing or additional testing process and under the additional conditions 2), 3), 4) and 5), which apply to item 13 (IB).

Additional conditions which apply to item 13 are:

1) The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column), no new impurities are detected;

2) appropriate testing of (re)validations are performed in accordance with relevant guidelines;

3) validation results show that updated test procedure is at least equivalent to the former test procedure;

4) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way;

5) The active substance, starting substances, intermediates or reagents are not biological substances;

14. Change of the manufacturer of active substance, starting substances, reagents or intermediates in the production procedure of active substance if the European Pharmacopoeia certificate of suitability has not been submitted:

a) if it is the change of currently approved manufacturing site of the same manufacturer (other or additional manufacturing site) and under additional conditions 1), 2) and 4) which apply to item 14 (IB);

b) if it is a new (other or additional manufacturer and under additional conditions 1), 2), 3) and 4) which apply to item 14 (IB).

Additional conditions which apply to item 14 are:

1) specifications (including process control, methods of analysis of all substances), manufacturing process (including the size of the scale batch) and detailed description of manner of synthesis are the same as those which have been already approved;

2) Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which a new assessment is required of viral safety or of TSE risk incompliance with the current criteria;

3) current or new manufacturer of active substance does not use the Drug master File (DMF);

4) change does not refer to the medicine which contains biologically active substance.

15. submitting of new or updated European Pharmacopoeia certificate of suitability for active substance, starting substances, reagents and intermediaries in the manufacturing process of active substance:

a) if the Certificate is submitted by already approved manufacturer and under additional conditions 1) 2) и 4) which apply to item 15 (IA);

b) if the Certificate is submitted by a new manufacturer:

I for sterile substances and under additional conditions 1), 2), 3) and 4) which apply to item 15 (IB)

II for other substances and under additional conditions 1), 2), 3) and 4) which apply to item 15 (IA)

c) if Certificate refers to substances for veterinary medicine, intended for treatment of animals susceptible to TSE risk and under additional conditions 1), 2), 3) and 4) which apply to item 15 (IB).

Additional conditions which apply to item 15 are:

1) specification for finished product during the marketing of the medicine batch and shelf life remain the same;

2) additional specifications (according to European Pharmacopoeia or National Pharmacopoeia) for impurities and other requests for finished medicine (e.g. particle size profiles, polymorphic form) remain the same;

3) active substances will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided;

4) The manufacturing process of the active substance, starting substances or reagents or intermediates does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

16. Submitting of new or updated TSE certificate (TSE European Pharmacopeia certificate of suitability) for active substance, starting substances, intermediates or reagents in the manufacturing procedure of active substance for currently approved manufacturer and approved manufacturing procedure:

a) for substances for medicine for veterinary use intended for treatment of animal susceptible to TSE risk (IB);

b) for other substances (IA).

17. Change:

a) of a retest period of active substance, under conditions 1), 2) and 3) which apply to item 17 (IB);

b) conditions for storage of active substance under the conditions 1) and 2) which apply to item 17 (IB).

Additional conditions which apply to item 17 are:

1) stability tests performed in accordance with currently approved protocol;

2) changes are not result of unexpected events during the time of manufacturing procedure and are not connected with the stability of product;

3) active substance is not biological substance.

18. Replacement of a single excipient with other comparative excipient (IB)

Additional conditions which apply to item 18 are:

1) functional characteristics of excipient remain the same;

2) disintegration time and time of release of active substance of new product which has been assessed in at least two pilot batches is comparable with the one already assessed in the previous product;

3) new excipient does not require the use of substances of human or animal origin for which an assessment of viral safety data is required. For excipients for veterinary medicines intended for treatment of animals susceptible to TSE risk, the risk shall be assessed by the Agency;

4) Medicine does not contain biologically active substance;

5) stability studies with at least two pilot batches or industrial scale batches are in progress and at least three months satisfactory stability data are at disposal of the applicant and the applicant undertakes that these studies will be finalised and that all results which are outside the specification limits at the end of the shelf life will be reported immediately to the Agency.

19. Change of specifications of excipients:

a) tightening of the specification limits and under additional conditions 1), 2) and 3) which apply to item 19 (IA); under additional conditions 2) and 3) which apply to item 19 (IB);

b) in the case of adding new specification parameter and under additional conditions 2), 4) and 5) which apply to item 19 (IB).

Additional conditions which apply to item 19 are:

1) change is not a result of obligation from previous assessment of specification limits approved in the procedure of obtaining of authorisation or later in the procedure of approval of variations type II;

2) change is not a result of unexpected events arising during manufacture;

3) changes are within currently approved specification limits;

4) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way;

5) changes do not refer to adjuvant for vaccines or biological excipients.

20. Change in the test procedure for an excipient:

a) Minor changes to an approved test procedure and under additional conditions 1), 2), 3) and 5) which apply to item 20 (IA);

b) minor changes to an approved test procedure for biological excipient and under additional conditions 1), 2), and 3) which apply to item 20 (IB);

c) other changes to test procedure, including the replacement of an approved test procedure with a new one and under additional conditions 2), 3), 4) and 5) which apply to item 20 (IB).

Additional conditions which apply to item 20 are:

1) analytical methods remain the same, without detecting new impurities;

2) appropriate (re)validation have been performed in accordance with relevant guidelines;

3) validation results show that updated test procedures are at least equivalent to the former test procedures;

4) any new test method does not concern a novel non-standard technique or a standard technique used in a novel way;

5) substance is not biological excipient.

21. Adjusting of new or updated certificate on harmonisation of excipient with European Pharmacopoeia:

a) if the certificate is submitted from currently approved manufacturer and under additional conditions 1), 2) and 3) which apply to item 21 (IA);

b) if the certificate from a new producer is submitted:

I for sterile substances and under additional conditions 1), 2), and 3) which apply to item 21 (IB)

II for other substances and under additional conditions 1), 2), and 3) which apply to item 21 (IA)

c) if the certificate is being submitted for substances which are integral part of the veterinary medicine intended for treatment of animals susceptible to TSE risk and under additional conditions 1), 2) and 3) which apply to item 21 (IB).

Additional conditions which apply to item 21 are:

1) specification of finished product during marketing of medicine and shelf life remain the same;

2) additional specifications (according to European Pharmacopoeia) for impurities and other requests for finished product (e.g. particle size profiles, polymorphic form) remain the same if relevant;

3) The manufacturing process of excipients does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

22. Adjusting of new or updated TSE certificate for excipient:

a) if the certificate is submitted from currently approved manufacturer or for new manufacture (IA);

b) if the certificate is submitted for excipient in veterinary medicine which is intended for animals susceptible to TSE risk (IB).

23. Change of TSE risky source of excipients or reagents into synthetic or herbal material:

a) if it is excipient or reagent which is used in manufacturing of biologically active substance or manufacturing of finished product which contains biologically active substance (IB);

b) in other cases (IA).

Conditions which apply to item 23 are that specifications for excipients and specifications for finished product during marketing of the medicine, as well as shelf life shell remain the same.

24. Change in synthesis or recovery of a non-pharmacopoeial excipient, when described in the documentation (IB)

Conditions which apply to item 24 is that there are no changes in qualitative and quantitative profile of impurities or in physicochemical characteristics of the medicine and that the excipient is not a biological substance.

25. Change is made to comply with European Pharmacopoeia or national pharmacopoeia:

a) change in specification of non-pharmacopoeial substance which is being harmonised with the European Pharmacopoeia or national pharmacopoeia:

I for active substance and under additional conditions 1) and 2) which apply to item 25 (IB),

II for excipient and under additional conditions 1) and 2) which apply to item 25 (IB)

b) change in pharmacopoeial substance which occurs due to harmonisation with the latest European Pharmacopoeia or national pharmacopoeia:

I for active substance and under additional conditions 1) and 2) which apply to item 25 (IA),

II for excipient and under additional conditions 1) and 2) which apply to item 25 (IA).

Conditions which apply to item 25:

1) the change is made to comply with European Pharmacopoeia or national pharmacopoeia,

2) specification for characteristics specific for the product remain the same (additionally to requests of pharmacopoeia), if relevant.

26. Change in specification of immediate packaging of finished product:

a) tightening of specification limits and under additional conditions 1), 2) and 3) which apply to item 26 (IA); under additional conditions 2) and 3) which apply to item 26 (IB);

b) in the case of addition of new testing parameter and under additional conditions 2) and 4) which apply to for item 26 (IB).

Additional conditions which apply to item 26:

1) change is not a result of obligation from previous assessment of specification limits approved in the procedure of obtaining of marketing authorisation for a medicine or later in the procedure of approval of variations type II;

2) change is not a result of unexpected events arising during manufacture;

3) changes are within currently approved specification limits;

4) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

27. Change in test procedure of immediate packaging of finished product:

a) in case of minor changes in currently approved test procedure and under additional conditions 1), 2) and 3) which apply for item 27 (IA);

b) other changes in test procedures including replacement or additional test procedures and under additional conditions 2) and 3) and 4) which apply to item 27 (IB).

Additional conditions which apply to item 27 are:

1) analytical methods remain the same;

2) appropriate (re)validation have been performed in accordance with relevant guidelines;

3) validation results show that updated test procedure is at least equivalent to the former test procedure;

4) any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

28. Changes of any part of immediate packaging which is not in contact with pharmaceutical form of finished product (IA)

Conditions which apply to item 28 are that the change which refers to that basic part of the material for packaging which influences the delivery, use, safety of finished product or its stability.

29. Change in qualitative and/or quantitative composition of immediate packaging:

a) for semisolid and liquid pharmaceutical forms and under additional conditions 1), 2), 3) and 4) which apply to item 29 (IB);

b) for other pharmaceutical forms and under additional conditions 1), 2), 3) and 4) which apply to item 29 (IA); under conditions 1), 3) and 4) (IB).

Additional conditions which apply to item 29 are:

1) product is not biological or sterile product;

2) change refers only to the same type of material for packaging (e.g. blister shall remain blister;

3) proposed material for packaging must be at least equivalent to currently approved material with regards to its relevant qualities;

4) stability studies with at least two pilot batches or industrial scale batches are in progress and at least three months satisfactory stability data are at disposal of the holder of authorisation and the holder of authorisation undertakes that these studies will be finalised and that all results which are outside the specification limits at the end of the shelf life will be reported immediately to the Agency.

30. Change (replacement, addition or deletion) of supplier of packaging or medicinal products which are integral part of the medicine, in accordance with submitted documentation, except for inhalers:

a) with deletion of suppliers and under additional condition 1) which applies to item 30 (IA);

b) with change or additional supplier and under additional conditions 1), 2), 3) and 4) which apply to item 30 (IB).

Additional conditions which apply to item 30 are:

1) no integral part of the packaging or medicinal product is deleted;

2) qualitative and quantitative composition of parts of packaging or medicinal product remains the same;

3) specification and control methods remain at least equivalent;

4) methods and conditions of sterilisation remain the same, in case of sterile product.

31. Change in the process control or value of limits which are valid in the manufacturing of medicine:

a) with tightening of process limits and under additional conditions 1), 2), and 3) which apply to item 31 (IA); under additional conditions 2) and 3) which apply to item 31 (IB);

b) with addition of new methods of control or values of limits and under additional conditions 2) and 4) which apply to item 31 (IB).

Additional conditions which apply to item 31 are:

1) change is not a result of obligation from previous assessment of specification limits approved in the procedure of obtaining of marketing authorisation or later in the procedure of approval of variations type II;

2) the change should not be the result of unexpected events arising during manufacture or because of stability concerns;

3) changes are within currently approved specification limits;

4) any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

32. Change in the size of scale batch of finished product:

a) if the size of the scale batch has been changed up to 10 times when compared to the size of the scale batch which was approved during obtaining of marketing authorisation for a medicine and under additional conditions 1), 2), 3), 4) and 5) which apply to item 32 (IA);

b) if the size of the scale batch has been reduced up to 10 times and under additional conditions 1), 2), 3), 4), 5) and 6) which apply to item 32 (IA);

c) in other situations and under additional conditions 1), 2), 3), 4), 5), 6) an 7) which apply to item 32 (IB).

Additional conditions which apply to item 32 are:

1) change does not affect reproductively and/or consistency of the product;

2) The change relates to standard immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms;

3) Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch-size;

4) Validation scheme is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines;

5) it does not relate to the medicine containing biologically active substance;

6) the change should not be the result of unexpected events arising during manufacture or because of stability concerns;

7) stability studies with at least one pilot batch or industrial scale batch are in progress and at least three months satisfactory stability data are at disposal of the holder of authorisation and the holder of authorisation undertakes that these studies will be finalised and that all results which are outside the specification limits at the end of the shelf life will be reported immediately to the Agency.

33. Minor change in manufacturing process of finished product (IB)

Conditions which apply to the item 33 are:

1) manufacturing principle remains the same;

2) The new process must lead to an identical product regarding all aspects of quality, safety and efficacy;

3) medicine does not contain biologically active substance;

4) with the change of the sterilisation procedure, change relates only to standard pharmacopoeial cycles;

5) stability studies with at least one pilot batch or industrial scale batch are in progress and at least three months satisfactory stability data are at disposal of the holder of authorisation and the holder of authorisation undertakes that these studies will be finalised and that all results which are outside the specification limits at the end of the shelf life will be reported immediately to the Agency.

34. Changes in colour (pigment) or means for correction of flavour:

a) in case of reduction or deletion of one or more components:

I of colour (pigment) under additional conditions 1), 2), 3), 4) and 7) which apply to item 34 (IA) or

II means for correction of flavour, under additional conditions 1), 2), 3), 4) and 7) which apply to item 34 (IA)

b) in case of increase, addition or replacement of one or more components:

I of colour (pigment) under additional conditions 1), 2), 3), 4), 5), 6) and 7) which apply to item 34(IB) or

II means for correction of flavour, under additional conditions 1), 2), 3), 4), 5), 6) and 7) which apply to item 34 (IB)

Additional conditions which apply to item 34 are:

1) No change in functional characteristics of the pharmaceutical form (e.g. disintegration time and release of active substance, dissolution profile);

2) Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product;

3) specifications of finished product are updated only regarding the look, smell and flavour, where relevant also the addition or cancellation of identification test;

4) Stability studies (accelerated ageing and in the planned shelf life) with at least two pilot batches or industrial scale batches are in progress and at least three months satisfactory stability data are at disposal of the proposer. Assurance is given that these studies will be finalised and that data will be provided immediately to the Agency if outside specifications or potentially outside specification at the end of the approved shelf life. In addition, where relevant, photo-stability testing should be performed;

5) Any new component must comply with regulations on colouring (pigments) or scent components;

6) Any new component does not include the use of materials of human or animal origin for which an assessment of viral safety data is required;

7) Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species are included.

35. Change in coating weight of oral dosage forms or change in weight of capsule shells:

a) Pharmaceutical forms with normal release of active substance and under additional conditions 1),3) and 4), which apply to item 35 (IA);

b) Gastro-resistant or modified pharmaceutical forms or pharmaceutical forms with prolonged release of active substance, and under additional conditions 1),2),3) and 4), which apply to item 35 (IB).

Additional conditions which apply to item 35 are:

1) The dissolution profile and release of active substance of the new product is determined on a minimum of two pilot scale batches is comparable to the old one. For herbal medicinal products where dissolution testing and testing of release of active substance may not be feasible, the disintegration time of the new product is comparable to the old one;

2) The coating is not a critical factor for the release mechanism;

3) The finished product specification has only been updated in respect of weight and dimensions, if applicable;

4) stability studies with at least two pilot batches or industrial scale batches are in progress and at least three months satisfactory stability data are at disposal of the holder of authorisation and the holder of authorisation undertakes that these studies will be finalised and that all results which are outside the specification limits at the end of the shelf life will be reported immediately to the Agency.

36. Change in shape or dimensions of the container or closure:

a) for sterile pharmaceutical forms or biological medicines and under additional conditions 1), 2) and 3) which apply to item 36 (IB);

b) for other pharmaceutical forms and under additional conditions 1), 2) and 3) which apply to item 36 (IA).

Additional conditions which apply to item 36 are:

1) No change in the qualitative or quantitative composition of the container;

2) The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product;

3) In case of a change in the headspace or a change in the surface/volume ratio, stability studies with at least two pilot scale (three for biological medicinal products) or industrial scale batches are in progress and at least three months (six months for biological medicinal products) stability data are at the disposal of the holder of authorisation. Assurance is given that these studies will be finalised and that data will be provided immediately to the Agency in case of outside specifications at the end of the approved shelf life.

37. Change in specification of finished product:

a) for tightening of specification limits, and under additional conditions 1),2) and 3), which apply to item 37 (IA) and under additional conditions 2) and 3) which apply to item 37 (IB);

b) for addition of new testing parameters and under additional conditions 2), 4) and 5) which apply to item 37 (IB).

Additional conditions which apply to item 37 are:

1) change is not a result of obligation from previous assessment of specification limits approved in the procedure of obtaining of marketing authorisation for a medicine or later in the procedure of approval of variations type II;

2) change is not a result to unexpected events arising during manufacture;

3) changes are within currently approved specification limits;

4) any new test method does not concern a novel non-standard technique or a standard technique used in a novel way;

5) test procedure do not relate to biologically active substance or biological excipient in the medicine.

38. Change in the test procedure of finished product:

a) Minor changes to an approved test procedure and under additional conditions 1), 2), 3), 4) and 5) which apply to item 38 (IA);

b) Minor changes to an approved test procedure of biologically active substance or biological excipient and under additional conditions 1), 2), 3) and 4), which apply to item 38 (IB);

c) Other changes to test procedures including replacement or addition of new test procedure and under additional conditions 2), 3), 4) and 5) which apply to item 38 (IB).

Additional conditions which apply to item 38 are:

1) analytical methods remain the same;

2) appropriate testing of (re)validations are performed in accordance with relevant guidelines;

3) validation results show that updated test procedure is at least equivalent to the former test procedure;

4) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way;

5) test procedures do not relate to biologically active substance or biological excipient in a medicine.

39. Change or addition of sign or marks on tablets (except for scoring/break line) or sign on capsules including replacement or addition of ink for product marking (IA)

Conditions which apply for item 39 are:

1) Finished product release and end of shelf life specifications have not been changed (except for appearance);

2) Any new ink must comply with the relevant pharmaceutical legislation.

40. Change in the size of the tablets, capsules, suppositories and pessaries without the change of qualitative or quantitative composition and average weight:

a) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses and under additional conditions 1) and 2) which apply to item 40 (IB);

b) Other pharmaceutical forms (tablets, suppositories or pessaries) and under other conditions 1) and 2) which apply to item 40 (IA).

Additional conditions which apply to item 40 are:

1) dissolution and release profile of the reformulated product is comparable to the old one. For herbal medicinal products, where dissolution and release testing may not be feasible, the disintegration time of the new product compared to the old one;

2) Finished product release and end of shelf life specifications have not been changed (except for size).

41. Change in the pack size of the finished product

a) Change in the number of units (e.g. number of tablets, ampoules etc.) in a pack:

I if the change is within the range of currently approved pack sizes and under additional conditions 1) and 2) which apply to item 41 (IA)

II if the change is outside the range of currently approved pack size and under additional conditions 1) and 2) which apply to item 41 (IB)

b) Change in the fill weight/fill volume of multidose medicinal products which are not for parenteral use and under additional conditions 1) 12) which apply to item 41 (IB).

Additional conditions which apply to item 41 are:

1) New pack size should be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics;

2) material of immediate packaging remains the same.

42. Change:

a) of the shelf life of finished product:

I as packaged for sale and under additional conditions 1), 2) and 3) which apply to item 42 (IB)

II after first opening and under additional conditions 1) and 2) which apply to item 42 (IB)

III after dilution or reconstitution and under additional conditions 1) and 2) which apply to item 42 (IB)

b) Change in storage conditions of the finished product or the diluted/reconstituted product and under additional conditions 1), 2) and 4) which apply to item 42 (IB).

Additional conditions which apply to item 42 are:

1) Stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met;

2) The change should not be the result of unexpected events arising during manufacture or because of stability concerns;
3) Shelf life is not longer than 5 years;
4) The product is not a biological medicine.

43. Addition, replacement or deletion of medical device for measuring or administration device which is not integrated part of immediate packaging (inhalers are excluded):
a) For medicine for human use:
I In case of addition or replacement and under additional conditions 1) and 2) which apply to item 43 (IA)
II In case of deletion and under additional condition 3) which applies to item 43 (IB).
b) For medicinal product for veterinary use and under additional conditions 1) and 2) which apply to item 43 (IB).
Additional conditions which apply to item 43 are:
1) The proposed measuring device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available;
2) The new medical device is compatible with the medicinal product;
3) The medicinal product can still be accurately delivered.

44. Change in specification parameters of a measuring or administration device for veterinary medicinal products:
a) Tightening of specification limits and under additional conditions 1), 2) and 3) which apply to item 44 (IA) and under additional conditions 2) and 3) which apply to item 44 (IB);
b) Addition of a new test parameter and under conditions from the item 2) and 4) which apply to this Article (IB).
Additional conditions which apply to the item 44 are:
1) change is not a result of obligation from previous assessment of specification limits approved in the procedure of obtaining of marketing authorisation for a medicine or later in the procedure of approval of variations type II;
2) change is not result of unexpected events arising during manufacture;
3) all changes are within the currently approved limits of specifications;
4) any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

45. Change in test procedure of a measuring or administration device for veterinary medicinal products:
a) Minor change to an approved test procedure and under additional conditions 1), 2) and 3) which apply to item 45 (IA);
b) Other changes to a test procedure including replacement of approved test procedure with new one, under additional conditions 2), 3) and 4) which apply to item 45 (IB).
Additional conditions which apply to item 45 are:
1) it is proven that the updated procedure is at least equivalent to the former procedure;
2) appropriate testing of (re)validations are performed in accordance with relevant guidelines;
3) validation results show that updated test procedure is at least equivalent to the former test procedure;
4) any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

46. Changes in the Summary of Product Characteristics of the essentially similar medicinal product (IB)
Conditions which apply to the item 46 are:
1) Proposed Summary of Product Characteristics is identical in important segments which are stated in the referral procedure to original product;
2) Application is submitted within 90 days from the day of publishing.

Annex 6

Agency for Medicines and Medical Devices of Montenegro

Number of the file:	Received by:
Date of reception:	Date of application with additional documentation:
Date of reception of additional documentation:	Date of complete application:

Filled in by the Agency for Medicines and Medical Devices of Montenegro

APPLICATION OF VARIATION / REQUEST FOR INTRODUCTION OF VARIATION

☐ Medicinal product for human use

☐ Medicinal product for veterinary use

Type IA and IB	☐
Type II	☐
Urgent safety measures (type II)	☐

BASIC DATA (to be filled-in in printed letters)[1]	
Name of medicine:	
Active substance/s (*INN*)	
Pharmaceutical form:	
Strength:	
Packaging:	

HOLDER OF MARKETING AUTHORISATION for a medicine	
Name of the company:	
Short name of the company:	
Address:	

MANUFACTURER:	
Name of the company:	
Address:	
Other manufacturing sites:	

PERSON RESPONSIBLE for obtaining marketing authorisation for a medicine	
Name, surname and title:	
Telephone.	
Telefax:	
E-mail:	
Number of marketing authorisation for a medicine:	
Date of issuance of marketing authorisation for a medicine:	
Marketing authorisation for a medicine is valid until:	

VARIATIONS TYPE I (mark the appropriate box)

	Variation

		IA	IB
1	Change of the name and/or address of the holder of authorisation if the holder remains the same legal person	☐	
2	Change of the name of the medicine not assuming the possibility of confusion with names of medicines which already have authorisation under protected or non-protected name		☐
3	Change of the name of active substance, if the active substance remains the same	☐	
4	Change of the name and/or address of manufacturer of active substance if European Pharmacopeia Certificate of Suitability has not been submitted, national or other recognised pharmacopeia and if the manufacturing site remains the same	☐	
5	Change of the name and/or address of manufacturer, if the manufacturing site remains the same	☐	
6	Change of ATC code or ATC vet. code after granting or change by WHO (IA).		
	a) Medicinal product for human use	☐	
	b) Medicinal product for veterinary use	☐	
7	Change or additional manufacturing site for part of production procedure or for all procedures of production of finished medicine:		
	a) change of the manufacturing site of outer packaging for all pharmaceutical forms	☐	
	b) Change of manufacturing site of immediate packaging		
	1. of solid pharmaceutical forms	☐	
	2. of semisolid or liquid pharmaceutical forms		☐
	3. of liquid pharmaceutical forms		☐
	c) change of the manufacturing site in which other production procedures are performed, except for marketing of the batch		☐
8	Change of conditions for marketing of batch and quality control of finished product		
	a) change or additional place of marketing of batch	☐	
	b) change of manufacturer or additional manufacturer responsible for marketing:		
	1. change does not include control of batch	☐	

	2. change includes control of batch	☐	
9	Deletion of any production site, including the site of production of active substance, semi-finished product, place of packaging, manufacturer which is responsible for marketing of the batch, place where the control of the batch is performed	☐	
10	Minor changes of the production process if active substance		☐
11	Change of the size of the scale batch in the production of active substance or intermediates:		
	a) if the size of the scale batch is increased 10 times when compared to the size of the scale batch which has been approved by obtaining marketing authorisation	☐	
	b) if the size of the scale batch is reduced	☐	
	c) if the size of the scale batch is increased o reduced more than 10 times when compared to the size of the scale batch which has been approved by obtaining marketing authorisation		☐
12	Change in the specification of active substance, starting material, intermediates or reagents which are used in the process of production of active substance:		
	a) tightening of specification limits	☐	☐
	b) addition of a new test parameter to the specification:		
	1. active substances		☐
	2. starting material, intermediates or reagents which are used in the process of production of active substance		☐
13	Change in test procedure of active substance or starting material, intermediates or reagents which are used in the procedure of production of active substance:		
	a) minor changes of already approves test procedure	☐	
	b) change in the test procedure which involves changes in the test procedure or additional test procedure		☐
14	Change of the manufacturer of active substance, starting material, reagents or intermediates in the production process of active substance if no European Pharmacopoeia certificate of suitability was submitted:		
	a) change of currently approved manufacturing site of the same manufacturer (other or additional manufacturing site)		☐
	b) new manufacturer (other or additional)		☐
15	Submission of new European Pharmacopoeia certificate of suitability for active substance, starting material, reagents or intermediates in the production process		

	of active substance:		
	a) by an approved manufacturer	☐	
	b) by a new manufacturer		
	1. for sterile substances		☐
	2. for other substances	☐	
	c) for substances for veterinary medicinal product intended for treatment of animals susceptible to TSE risk (Transmissible spongiform encephalopaties)		☐
16	Submission of new or updated TSE certificate (TSE European Pharmacopoeia certificate of suitability) for active substance, starting material, intermediates or reagents in the production procedure of active substance for currently approved manufacturer and currently approved production procedure:		
	a) for substances which are integral part of veterinary medicinal products intended for treatment of animals susceptible to TSE risk		☐
	b) for other substances	☐	
17	Change:		
	a) of the period of retesting of active substance		☐
	b) conditions for storage of active substance		☐
18	Replacement of a single excipient with other comparative excipient		☐
19	Change of specification of excipients		
	a) tightening of specification limits	☐	☐
	b) additional of new specification parameter		☐
20	Change in the test procedure for an excipient		
	a) minor changes in currently approved test procedure	☐	
	b) minor changes in currently approved test procedure for biological excipient		☐
	c) other changes in the test procedure, including replacement of already approved test procedure with a new one		☐
21	Submission of new or updated European Pharmacopoeia certificate of suitability:		
	a) by an approved manufacturer	☐	

	b) by new manufacturer		
	1. for sterile substances		☐
	2. for other substances	☐	
	c) for substances which are integral part of veterinary medicinal products intended for treatment of animals susceptible to TSE risk		☐
22	Submission of new or updated TSE certificate for excipient:		
	a) by an approved manufacturer or for new manufacturer	☐	
	b) for excipient in veterinary medicinal product intended for treatment of animals susceptible to TSE risk		☐
23	Change of TSE risky source of excipients or reagents into synthetic or herbal material:		
	a) if it is excipient or reagent which is used in manufacturing of biologically active substance or manufacturing of finished product which contains biologically active substance		☐
	b) other	☐	
24	Change in synthesis or recovery of a non-pharmacopoeial excipient, when described in the documentation		☐
25	Change is made to comply with European Pharmacopoeia or national pharmacopoeia		
	a) change in specification of non-pharmacopoeial substance which is being harmonised with the European Pharmacopoeia or national pharmacopoeia		
	1. change of active substance		☐
	2. change of excipient		☐
	b) change in pharmacopoeial substance which occurs due to harmonisation with the latest European Pharmacopoeia or national pharmacopoeia		
	1. change of active substance	☐	
	2. change of excipient	☐	
26	Change in specification of immediate packaging of finished product		
	a) tightening of specification limits	☐	☐
	b) addition of a new test parameter to the specification		☐

27	Change in test procedure of immediate packaging of finished product		
	a) minor changes in currently approved test procedure	☐	
	b) other changes to test procedure including replacement or additional test procedures		☐
28	Changes of any part of immediate packaging which is not in contact with pharmaceutical form of finished product	☐	
29	Change of quantitative and/or qualitative composition of immediate packaging		
	a) for semisolid and liquid pharmaceutical forms		☐
	b) for all other pharmaceutical forms	☐	☐
30	Change (replacement, addition or deletion) of supplier of packaging or medicinal products which are integral part of the medicine, in accordance with submitted documentation, except for inhalers:		
	a) deletion of supplier	☐	
	b) replacement or addition of supplier		☐
31	Change in the process control or value of limits which are valid in the manufacturing of medicine:		
	a) tightening of process limits	☐	☐
	b) addition of new methods of control or values of limits		☐
32	Change in the size of scale batch of finished product:		
	a) the size of the scale batch has been changed up to 10 times when compared to the size of the scale batch which was approved during obtaining of marketing authorisation for a medicine	☐	
	b) the size of the scale batch has been reduced up to 10 times	☐	
	c) other change of a scale batch		☐
33	Minor change in manufacturing process of finished product		☐
34	Changes in colour (pigment) or means for correction of flavour		
	a) reduction or deletion of one or more components		
	1. colour (pigment)	☐	
	2. means for correction of flavour	☐	
	b) increase, addition or replacement of one or more components:		

	1. colour (pigment)		☐
	2. means for correction of flavour		☐
35	Change in coating weight of oral dosage forms or change in weight of capsule shells		
	a) Pharmaceutical forms with normal release of active substance	□	
	b) Gastro-resistant or modified pharmaceutical forms or pharmaceutical forms with prolonged release of active substance		□
36	Change in shape or dimensions of the container or closure		
	a) for sterile pharmaceutical forms or biological medicines		☐
	b) for other pharmaceutical forms	☐	
37	Change in specification of finished product:		
	a) for tightening of specification limits	☐	☐
	b) for addition of new testing parameters		☐
38	Change in the test procedure of finished product:		
	a) Minor changes to an approved test procedure	☐	
	b) Minor changes to an approved test procedure of biologically active substance or biological excipient		☐
	c) Other changes to the a test procedure including replacement or addition of new test procedure		☐
39	Change or addition of sign or marks on tablets (except for scoring/break line) or sign on capsules including replacement or addition of ink for product marking	☐	
40	Change in the size of the tablets, capsules, suppositories and pessaries without the change of qualitative or quantitative composition and average weight		
	a) Gastro-resistant, modified or prolonged release pharmaceutical forms		☐
	b) Other pharmaceutical forms (tablets, suppositories or pessaries)	☐	
41	Change in the pack size of the finished product		
	a) Change in the number of units (e.g. number of tablets, ampoules		

	etc.) in a pack		
	1. the change is within the range of currently approved pack sizes	☐	
	2. the change is outside the range of currently approved pack sizes		☐
	b) Change in the fill weight/fill volume of multidose medicinal products which are not for parenteral use		☐
42	Change:		
	a) of the shelf life of finished product		
	1. as packaged for sale		☐
	2. after first opening		☐
	3. after dilution or reconstitution		☐
	b) Change in storage conditions of the finished product or the diluted/reconstituted product		☐
43	Addition, replacement or deletion of medical device for measuring or administration device which is not integrated part of primary packaging (inhalers are included)		
	a) medicinal product for human use		
	1. addition or replacement	☐	
	2. deletion		☐
	b) medicinal product for veterinary use		☐
44	Change in specification parameters of a measuring or administration device for veterinary medicinal products		
	a) Tightening of specification limits	☐	☐
	b) Addition of new test parameters		☐
45	Change in test procedure of a measuring or administration device for veterinary medicinal products		
	a) Minor changes to an approved test procedure	☐	
	b) Other changes to a test procedure including replacement of approved test procedure with new one		☐
46	Changes in the Summary of Product Characteristics of the essentially similar medicinal (for human or veterinary use)		☐

VARIATIONS TYPE II

A. Variations in the part I of documentation (EU file) Variations in the module 1 and 2 (CTD file)	☐	part (i) _____ pages _____	Expert report[2] Amended ☐ Added ☐
B. Variations in the part II of documentation (EU file) Variations in the Module 3 (CTD file)	☐	part(i) _____ pages _____	
C. Variations in the part III of documentation (EU file) Variations in the Module 4 (CTD file)	☐	part(i) _____ pages _____	
D. Variations in the part IV of documentation (EU file) Variations in the Module 5 (CTD file)	☐	part(i) _____ pages _____	

Concise description of variation:

Variations type I, which are processed according to the procedure for variations type II *(mark the relevant answer)*:

☐ variations of immunological medicines — No:

☐ variations of medicines from blood and plasma — No:

☐ variations of radio-pharmaceutical medicines — No:

☐ variations of biotechnological medicines — No:

MAIN VARIATION[3] (In case of consequential variations)
Main variation is stated in that request under the number _____ (1 to 45)

Short description of reason for the proposed variation[4]:

CURRENT STATE	PROPOSAL

Changed Anatomical-Therapeutic-Chemical mark (ATC) or ATC vet, if necessary

I hereby declare, that the stated variation shall not affect the quality, efficiency and safety of the medicine, and that submitted data substantiate the proposed variation. I declare that there are no other unreported variations in the remaining documentation.
Name, surname and title of responsible person _____ _____ Date Signature of responsible person

[1] Form should be filled-in separately for each pharmaceutical form and strength

[2] In case that expert report is not submitted in the process of acquiring marketing authorisation for a medicine, opinion of an expert regarding the request for variation shall be added; amended expert opinion on variation shall refer to already submitted expert report.

[3] More consequential variations may be included in one request if you marked more variations (1-46). Main variation has to be clearly stated. Reason for consequential variations must be described in the concise reason for proposed variation. If variations are not consequential it is necessary to submit for each separately new request.

[4] Explain already approved and proposed text or specification. With changes in the Summary Product Characteristics and instruction for patient, underline or clearly mark in different letters all changed words or add the whole new version of text.

ANNEX 7

LIST OF VARIATIONS WHICH REPRESENT WIDENING OF MARKETING AUTHORISATION FOR A MEDICINE FOR WHICH A NEW REQUEST IS REQUIRED

Changes for which is required new request for issuance of marketing authorisation for a medicine are:

- variations which refer to active substance/s;
- variations which refer to change of strength, pharmaceutical form and way of use and
- variations which are characteristic for veterinary medicinal product for animals for human consumption.

Variations which refer to active substance/s are:

- additional active substance, including antigens vaccine;
- removal of active substance, including antigen vaccine;
- change of quantity of active substance;
- new form of active substance (e.g. new form of salt, ester and other derivatives), while the structure remains the same with therapeutic effect, and characteristics regarding safety/efficiency of medicine have not been significantly changed;
- replacement of active substance with other isomer, other complex, change of recemate with one enantiomer, whereas the characteristics regarding safety/efficiency of medicine have not been significantly changed;
- replacement of biological substance or biotechnological product with other different product with slightly different molecular structure; change of vector which is used for making biotechnological material or change of the source of the cell bank, whereas the characteristics regarding safety/efficiency of the medicine have not been significantly changed;
- new ligand or binding mechanism with radio-pharmaceutical products and
- change of extraction solvent or ratio herbal drug/herbal preparation, whereas the characteristics regarding safety/efficiency of the medicine have not been significantly changed.

Variations which refer to the change of strength, pharmaceutical form or way of use of medicine:

- changes of bio-availability;
- changes in pharmacokinetics e.g. in the release time;
- changes in strength or additional strength of a medicine;
- change of pharmaceutical form or additional pharmaceutical form and
- change or new way of use of medicine (in parenteral use, it is necessary to make a larger distinction between intra-arterial, intravenous, intramuscular, subcutaneous and others).

Annex 8

form

Agency for Medicines and Medical Devices of Montenegro

Number of application Control number:	Received by:
Date of reception:	Date of application with additional documentation:
Date of reception of additional documentation:	Date of complete application:

Filled-in by the Agency for Medicines and Medical Devices of Montenegro

REQUEST FOR TRANSFER OF AUTHORISATION TO NEW HOLDER OF AUTHORISATION

☐ Medicinal product for human use

☐ Medicinal product for veterinary use

BASIC DATA (to be filled-in in printed letters)[1]	
Name of the medicine:	
Active substance/s (*INN* in official language):	
Pharmaceutical form:	
Strength:	
Packaging:	
MANUFACTURER:	
Name of the company:	
Address:	
Other production sites:	
CURRENT HOLDER OF MARKETING AUTHORISATION for a medicine	
Name of the company:	
Short name of the company:	
Address:	
PERSON RESPONSIBLE for obtaining marketing authorisation for a medicine	
Name, surname and title:	
Telephone:	

Telefax:	
E-mail:	
PERSON RESPONSIBLE for pharmacovigilance	
Name, surname and title:	
Telephone:	
Telefax:	
E-mail:	
NEW HOLDER OF MARKETING AUTHORISATION for a medicine	
Name of the company:	
Short name of the company:	
Address:	
PERSON RESPONSIBLE for obtaining marketing authorisation for a medicine	
Name, surname and title:	
Telephone:	
Telefax:	
E-mail:	
PERSON RESPONSIBLE for pharmacovigilance[2]	
Name, surname and title:	
Telephone:	
Telefax:	
E-mail:	

Current *EAN* code:

Shall the EAN code be changed with the change of holder of marketing authorisation for a medicine?

YES ☐ NO ☐

New *EAN* code:

Envisaged date of transfer of marketing authorisation for a medicine to new holder:

[1] Form should be filled-in separately for each pharmaceutical form and strength.
[2] If the responsible person for marketing of a medicine is also the responsible person for pharmacovigilance, the same data should be repeated.

STATEMENT OF THE NEW HOLDER OF MARKETING AUTHORISATION FOR A MEDICINE

I hereby declare:

- that I accept the transfer of marketing authorisation for the abovementioned medicine;
- that I accept all rights and obligations for abovementioned medicine;
- that I accept the whole documentation of the medicine, including all authorizations and other legal documents which refer to abovementioned medicine.

Name, surname and title of responsible person

_____ _____

Date Signature of responsible person

STATEMENT OF THE CURRENT HOLDER OF MARKETING AUTHORISATION FOR A MEDICINE

I hereby declare:

- that we are transferring the marketing authorisation for abovementioned medicine to the new holder and at the same time we request the termination of the marketing authorisation for a medicine number .....;
- that we transfer all our rights and obligations to the new holder;
- that we allow the transfer of the whole documentation to the new holder, including all authorisations and other legal documents which refer to the abovementioned medicine.

Name, surname and title of responsible person

_____ _____

Date Signature of responsible person

Annex 9

form

Agency for Medicines and Medical Devices of Montenegro

Number of the file:	Received by:
Date of reception:	Date of application with additional documentation:
Date of reception of additional documentation:	Date of complete application:

Filled in by the Agency for Medicines and Medical Devices of Montenegro

APPLICATION FOR RENEWAL OF MARKETING AUTHORISATION FOR A MEDICINE

☐ Medicinal product for human use

☐ Medicinal product for veterinary use

BASIC DATA (to be filled-in in printed letters)[1]	
Name of the medicine:	
Active substance/s (*INN* in official language):	
Pharmaceutical form:	
Strength:	
Packaging:	
MANUFACTURER:	
Name of the company:	
Address:	
Other manufacturing sites:	
HOLDER OF MARKETING AUTHORISATION for a medicine	
Name of the company:	

Short name of the company:	
Address:	
PERSON RESPONSIBLE for obtaining the marketing authorisation for a medicine	
Name, surname and title:	
Telephone:	
Telefax:	
E-mail:	
Number of marketing authorisation for a medicine:	
Date of issuance of marketing authorisation for a medicine:	
Marketing authorisation for a medicine is valid until:	

Has the medicine been the whole time on the market in Montenegro: YES ☐ NO ☐
Explanation:

LIST OF VARIATIONS

Chronological list, dates of licences for introduction of variation or application and short description of variations, which were introduced from last renewal or from issuance of marketing authorisation for a medicine, in case of first renewal.

Date	Short description
1.	

2.
3.
4.
5.

REMARK: Make the photocopy of the page if necessary

DOCUMENTS WHICH ARE SUBMITTED WITH THE REQUEST FOR RENEWAL OF MARKETING AUTHORISATION FOR A MEDICINE[2]

Summary of Product Characteristics – already approved	☐
Summary of Product Characteristics – changed, if necessary	☐
Instruction for patient or user – already approved	☐
Instruction for patient or user – changed, if necessary	☐
Packaging – already approved	☐
Proposal of change of packaging, if required by variation	☐
Amended or additional expert report for pharmaceutical-chemical-biological part of documentation	☐
Amended or additional expert report for pharmacological-toxicological part of documentation	☐
Amended or additional expert report for clinical part of the documentation	☐
Last Periodic Safety Update Report of medicine *(PSUR)* OR REFERENCE TO ALREADY SUBMITTED PSUR IN ACCORDANCE WITH THE	☐

HARMONISED DYNAMICS OF SUBMISSION OF PSUR	
Summary Bridging Report	☐
Additional report on safety (Addendum Report)	☐
***GMP* certificate**	☐
Or statement of competent authority, that the submitted certificate is still valid	☐
Other relevant documents, to be stated:	☐

I hereby declare, that all data on medicine, except for data which are listed as approved or registered variations, are unchanged since obtaining of the marketing authorisation for a medicine.
Name, surname and title of responsible person
_____ Date _____ Signature of responsible person

[1] Form should be filled-in separately for each pharmaceutical form and strength
[2] Mark the attached documents

Annex 10

form

Agency for Medicines and Medical Devices of Montenegro

Number of request Control number:	Received by:
Date of reception:	Date of application with additional documentation:
Date of reception of additional documentation:	Date of complete application:

Filled-in by the Agency for Medicines and Medical Devices of Montenegro

REQUEST FOR TERMINATION OF VALIDITY OF MARKETING AUTHORISATION FOR A MEDICINE

☐ Medicinal product for human use

☐ Medicinal product for veterinary use

BASIC DATA (to be filled-in in printed letters)[1]	
Name of the medicine:	
Active substance/s (*INN* in official language):	
Pharmaceutical form:	
Strength:	
Packaging:	
HOLDER OF MARKETING AUTHORISATION for a medicine	
Name of the company:	
Short name of the company:	
Address:	
PERSON RESPONSIBLE for obtaining marketing authorisation for a medicine	
Name, surname and title:	
Telephone:	
Telefax:	
E-mail:	
Number of marketing authorisation for a medicine:	
Date of issuance of marketing authorisation for a medicine:	
Marketing authorisation for a medicine is valid until:	

MANUFACTURER:	
Address:	
Other manufacturing sites:	
Name of the company:	

Has the medicine been the whole time on the market in Montenegro: YES ☐ NO ☐
Explanation:

Reason for Request for termination of validity of marketing authorisation:

Name, surname and title of responsible person
_____ _____ Date Signature of responsible person

[1] Form should be completed separately for each pharmaceutical form, strength and packaging