

Rules on Procedure and Requirements for the Marketing Authorization for Medicinal Product Granting

("The Official Gazette of the Republic of Serbia", No. 93/2005)

I INTRODUCTORY PROVISION

Article 1

This Rules establishes the contents of an application, procedure and requirements for the marketing authorization for medicinal product (hereinafter referred to as: authorization) granting, and the contents of the documentation required; conditions and documentation required for the marketing authorization issuing on the base of abbreviated applications; conditions, documentation, mode, and procedure for the marketing authorization amending (hereinafter referred to as: variations), and the procedure and contents of a dossier required for the marketing authorization renewal.

II THE CONTENTS OF THE APPLICATION, PROCEDURE AND CONDITIONS FOR THE AUTHORIZATION GRANTING AND THE CONTENTS OF THE DOCUMENTATION SUBMITTED

Article 2

Application for the marketing authorization granting shall be submitted to the Medicines and Medical Devices Agency of Serbia (hereinafter referred to as: the Agency).

The applicant may be:

- 1) A manufacturer of medicinal products holding a license to manufacture medicinal products in the Republic of Serbia;
- 2) A manufacturer's representative or an agent with a seat in the Republic of Serbia.

The applicant referred to in paragraph 2 of this Article shall have in the employ a person responsible for the authorization obtaining, amending and/or renewal.

A person responsible referred to in paragraph 3 of this Article shall be accountable for the accuracy of data on the medicinal product quality, safety and efficacy contained in the documentation for the authorization obtaining, amending and/or renewal.

Article 3

The application for a marketing authorization shall include:

UNREVISED VERSION

- 1) A cover letter;
- 2) Properly completed application form;
- 3) Documentation on the medicinal product required under this Rules;
- 4) Evidence of fees paid.

Each application for authorization submitted to the Agency shall be accompanied by the medicinal product sample the amount of which shall be appropriate for the repeated laboratory quality control of the medicinal product; the responsibility for the delivery of samples rests with the applicant.

The application form referred to in paragraph 1 clause 2) of this article shall be submitted for each pharmaceutical form, strength and package size.

The application form referred to in paragraph 1 clause 2) of this article is appended herewith and constitutes an integral part of this Rules (Form No. 1).

Article 4

A cover letter referred to in article 3 paragraph 1 clause 1) of the Rules shall include:

- 1) Logo, name and address of the applicant;
- 2) Subject of application;
- 3) The medicinal product name (proprietary, INN or generic name, pharmaceutical form, strength) with relevant information;
- 4) Proposed package size and label;
- 5) The name of manufacturer;
- 6) Proposed *ATC* (anatomical-therapeutical-chemical) classification code, or veterinary *ATC* classification code for medicinal product for veterinary use;
- 7) Common drug classification code (JKL);
- 8) Proposed legal category (prescription-only or prescription-free);
- 9) Date and signature of the person responsible for the authorization issuing procedure.

The cover letter referred to in paragraph 1 of this article can cover more than one application for the authorization granting.

UNREVISED VERSION

Article 5

The documentation on the medicinal product referred to in article 3, paragraph 1 clause 3) herein shall be submitted to the Agency in the form of a hard copy, in the official language and script of the Republic of Serbia.

The documentation on the medicinal product referred to in paragraph 1 of this article can also be submitted in the form of electronic document.

May the applicant opt for the submission of the electronic documentation on the medicinal product, he/she shall enclose a duly signed statement claiming that he/she will, if required by the Agency and not later than within 30 days from the submission of electronic documentation on the medicinal product, make a hard copy of the documentation submitted available to the Agency.

The applicant may also submit the documentation on the medicinal product in the form of the original dossier photocopy, except in cases where the submission of an original documentation on the medicinal product has been stipulated by this Rules.

In case of the applicant submitting the documentation on the medicinal product in the form of the original dossier photocopy, he/she shall testify in writing that the photocopy is a true and reliable copy of the original dossier.

The documentation on the medicinal product referred to in article 3 paragraph 1 clause 3) herein can be submitted in the English language as one of official languages used in the Community; however, the proposed Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), and the proposed primary and secondary packaging of the medicinal product shall be submitted to the Agency solely in the official language and script of the Republic of Serbia.

The documentation on the medicinal product shall be submitted further to the Agency request in not more than two identical copies.

Article 6

The Agency shall only take into consideration such application that contains all particulars and documents referred to in article 3 herein, as such an application shall be regarded complete according to this Rules.

Not later than 60 days from the date of submission the Agency shall determine if the application is complete and inform the applicant in writing if the application is complete or inadequate.

In case of an inadequate application and upon the request of the Agency, the applicant shall provide the particulars and documents missing within 30 days from the date of notification referred to in paragraph 2 of this article.

UNREVISED VERSION

May the applicant fail to provide the stipulated particulars and documents within the time frame referred to in paragraph 3 of this article, the Agency shall reject his/her application for the authorization granting as inadequate.

Article 7

Once the Agency decides that the application submitted is complete the 210-day time limit within which the Agency shall decide on the authorization granting or refusal is activated.

The time limit laid down in paragraph 1 of this article shall be counted from the date the applicant has been notified in writing by the Agency that his/her application is complete. .

Within the time period referred to in paragraph 1 of this article the Agency shall issue an authorization to the applicant as the holder of the authorization for the medicinal product for which the application has been submitted.

Article 8

Once the completeness of the application is established the Agency shall perform scientific evaluation of the documentation on the medicinal product.

In the course of scientific evaluation of the documentation on the medicinal product, the Agency may ask in writing that the applicant provide supplementary information or documentation needed for evaluation of the medicinal product quality, safety and efficacy.

May the applicant fail to provide the particulars and documents referred to in paragraph 2 of this article within 180 days after receipt of a written notification from the Agency, the Agency shall reject the application for authorization on the grounds of failure to establish quality, safety or efficacy of the medicinal product.

In the case referred to in paragraph 2 of this article the time limit of 210 days for the authorization granting shall be suspended the day the Agency issues the request for supplementary data to the applicant, and shall be resumed the day the supplementary data requested have been provided.

Authorization granting

Article 9

The applicant may be granted authorization on the basis of documentation constituting a part of the application for an authorization and including at least:

- 1) Administrative particulars and documents comprising the name of the medicinal product, *INN*, generic name or chemical formula of the active pharmaceutical ingredient,

UNREVISED VERSION

pharmaceutical form and strength of the medicinal product considered, proposed Summary of Product Characteristics, proposed Patient Information Leaflet, name and address of the applicant for the authorization granting, name and address of the manufacturer, identification of the manufacturing site, proposed primary and secondary packaging, proof that the medicinal product has a marketing authorization in the country of origin and that it is actually marketed in the country where it is being manufactured, the list of countries in which the medicinal product is already authorized, etc.;

2) Pharmaceutical and chemical and biological particulars on the qualitative and quantitative composition of the medicinal product, (brief) process description, i.e. development pharmaceuticals, quality control of all starting materials, in-process quality control, quality control of the finished medicinal product, stability studies, and on the assessment of the environmental safety;

3) Pharmacological and toxicological particulars on pharmacodynamic and pharmacokinetic properties of the medicinal product, toxicity data, effect on reproduction, data on embryo-fetal and perinatal toxicity, mutagenicity and carcinogenic potential, and data on local tolerance, as well, or in case of the medicinal product for veterinary use the data on withdrawal period and maximum levels of residues;

4) Clinical data containing general information the study, data on study performance, study results, clinical and pharmacological data, bioavailability and/or bioequivalence data where required, clinical safety and efficacy data, documents on special events observed during the study and on experience accumulated by the post-authorization surveillance in other countries.

Article 10

The documentation referred to in article 9 herein the applicant shall submit as:

1) His/her proprietary documentation on pharmaceutical, chemical and biological, pharmacological and toxicological, and clinical drug studies, incorporating all parts required;

2) His/her proprietary documentation on pharmaceutical/chemical-biological study together with the literature data on pharmacological and toxicological and clinical drug studies, published in scientific publications and containing all parts required;

3) His/her proprietary documentation on pharmaceutical, chemical and biological study combined with joint data (both proprietary and literature data), data on pharmacological and toxicological and clinical drug studies published in scientific literature and containing all parts required.

In case of pharmacological and toxicological and/or clinical data from the documentation referred to in paragraph 1 clause 2) of this article the description of which cannot be found in scientific publications, a scientific rationale can be submitted in lieu of such

UNREVISED VERSION

information, claiming well established safety and efficacy of the ingredients involved, proved safety and efficacy of the medicinal product, namely claiming that the absence of data does not affect final assessment of the medicinal product safety and efficacy, as confirmed by the appropriate expert report.

The submission of an application containing data referred to in paragraph 1 of this article shall only be possible if it can be demonstrated that the active substance has been in well established medicinal use within the Republic of Serbia, the European Union and/or other countries specifying the same requirements for the marketing authorization granting for at least ten years.

In the procedure of the marketing authorization granting the Agency may also call for other data relevant to the authorization issuing according to the Law on Medicinal Products and Medical Devices ("The Official Gazette of the Republic of Serbia", No. 84/04 – hereinafter referred to as: the Law), and in compliance with the regulations governing enforcement of the Law.

Article 11

The expert report on certain parts of the documentation on the medicinal product quality, safety and efficacy (hereinafter referred to as: expert report) shall include:

- 1) Information on the expert issuing such an expert report;
- 2) Abbreviated Summary of Product Characteristics consisting of one to two pages referring to:
 - 2.1. Application type (new active pharmaceutical substance, new combination of active substances, essentially similar medicinal product, new pharmaceutical form, strength or indication, etc.),
 - 2.2. Chemical and pharmacokinetic parameters,
 - 2.3. Indications,
 - 2.4. Warnings,
 - 2.5. Pharmacovigilance data;
- 3) The expert report including references to certain parts of the documentation or literature data to which such an expert report refers, including:
 - 3.1. Medicinal product quality data (app. 10 pages),
 - 3.2. Medicinal product safety data (app. 25 pages),
 - 3.3. Medicinal product efficacy data (app. 25 pages);
- 4) Written or tabular summary of the expert report with the conclusion prepared by the expert report issuing authority;
- 5) The applicant's statement on the interrelation with the expert report issuing authority;
- 6) Supplement to the Expert Report, as required;
- 7) Signature of the expert issuing the Expert Report;

8) Date issued.

Article 12

Documentation for the authorization granting for medicinal products for human use shall include administrative data, pharmaceutical, chemical and biological study data, pharmacological and toxicological study data, and clinical study data, as well.

Documentation for the authorization granting for medicinal products for veterinary use only shall include administrative data, pharmaceutical, chemical and biological study data, safety data and residue study data, together with data on preclinical and clinical studies of a veterinary medicinal product.

Documentation for the authorization granting for an immunological medicinal product for veterinary use only shall include administrative data, pharmaceutical, chemical and biological and microbiological study data, drug safety study data, and data on the efficacy of such veterinary immunological medicinal product.

Article 13

A marketing authorization can also be issued on the basis of an abbreviated documentation.

The applicant as shall submit the abbreviated documentation referred to in paragraph 1 of this article:

- 1) The applicant's proprietary data on the pharmaceutical, chemical and biological testing of the medicinal product;
- 2) Detailed reference or a reference to the data on pharmacological and toxicological and clinical studies of a medicinal product that is essentially similar to the medicinal product covered by the application.

The application and documentation referred to in paragraph 1 of this article, shall be supported by:

- A proof of essential similarity of the medicinal product and/or proof that the authorization holder of the reference product has consented that the pharmacological and toxicological part of the dossier of that product is used for the purpose of examining the application in question, or

- A proof that the reference medicinal product essentially similar to the medicinal product covered by the application has, at the time of the application submitting, been marketed in the Republic of Serbia, the European Union and/or other countries specifying the same requirements for the authorization granting for not less than six years and for not less than ten years where a biotechnological medicinal product is concerned.

UNREVISED VERSION

In addition to proofs referred to in paragraph 3 of this article, the applicant shall also submit proof that both medicinal products are compliant with the summary of product characteristics, patient information leaflet and labeling of the medicinal product concerned.

Article 14

A generic medicinal product may be authorized on the base of documentation referred to in paragraph 13 herein six years from the first authorization for the reference medicinal product issued, and ten years from the first authorization of a biotechnological reference medicinal product.

Article 15

A generic, i.e. essentially similar medicinal product is, in the meaning of this Rules, a medicinal product having the same qualitative and quantitative composition in the same pharmaceutical form as the originator product, whose bioequivalence is comparable with that of the reference medicinal product and been demonstrated by appropriate bioavailability studies.

The reference medicinal product is, in the meaning of this Rules, the first medicinal product of the kind authorized in the European Union and regarded as the originator medicinal product.

Article 16

If the applicant submits the application for authorization of the medicinal product containing fixed combination of active substances used in the composition of medicinal products authorized in the Republic of Serbia, the European Union and/or other countries specifying the same requirements for the authorization granting, but not hitherto used in combination for therapeutic purposes, the documentation shall relate to the combination, and not to each individual active substance.

Structure and contents of the documentation supporting application for authorization

Article 17

The documentation on the medicinal product referred to in article 3, paragraph 1, clause 3) herein for the medicinal product for human use shall be submitted in the Common Technical Document format (hereinafter referred to as: CTD dossier) or in the European format (hereinafter referred to as: European dossier) under the conditions stipulated by this Rules.

The documentation on the medicinal product referred to in article 3, paragraph 1, clause 3) herein for the veterinary medicinal product, that is, on the immunological medicinal

UNREVISED VERSION

product for the sole use in veterinary medicine, shall be submitted in the form of an European dossier, under the conditions stipulated by this Rules.

A. Documentation presented in a CTD dossier

Article 18

The CTD dossier referred to in article 17, paragraph 1 herein consists of four separate parts relating to common general requirements and to specific requirements, with appropriate documentation for specific groups of medicinal products and relevant to their properties and origin of active substances, that shall be processed and adapted in specific way.

Part I of the CTD dossier

Article 19

Part I of the CTD dossier comprises common general requirements the documentation being presented in the module form, namely:

Module 1 - Administrative and regional data;

Module 2 - Summary expert reviews of the Modules 1, 2, and 5;

Module 3 - Quality data (pharmaceutical, chemical and biological data on medicinal products containing active substance of chemical or biological origin);

Module 4 - Preclinical drug trials;

Module 5 - Clinical drug trials.

Article 20

Module 1 referred to in article 19 herein comprises administrative and regional data, namely:

1.1 A detailed review of the CTD documentation contents;

1.2 Properly completed application form;

1.3 Proposed summary of product characteristics, proposed patient information leaflet, proposed primary and secondary packaging and labeling:

1.3.1 Proposed summary of product characteristics,

1.3.2 Proposed patient information leaflet,

1.3.3 Proposed primary and secondary packaging and labeling,

1.3.4 Proposed summary of product characteristics to be used in other countries;

1.4 Information on the expert (CV with references, connection to the applicant, signatures of experts);

UNREVISED VERSION

1.5 Specific requirements:

- 1.5.1 Information required for bibliographical application,
- 1.5.2 Information required for abridged application (dependent/generic application);

1.6 Environmental risk assessment.

In addition to information referred to in paragraph 1 of this article, Module 1 comprises two appendices relating to the environmental risk assessment and evidence of therapeutic usefulness in case of orphan medicinal products.

The particulars and documents referred to in article 30 herein may be required by the Agency as regional particulars and documents referred to in paragraph 1 of this article.

Article 21

Module 2 referred to in article 19 herein comprises summary expert reviews on Modules 3, 4 and 5, namely:

- 2.1 Module 2 table of contents;
- 2.2 Introduction;
- 2.3 Comprehensive summary of product quality;
- 2.4 Overview of preclinical investigation or documentation;
- 2.5 Overview of clinical investigation or documentation;
- 2.6 Summary of preclinical investigation or documentation:
 - 2.6.1 Summary of pharmacological information,
 - 2.6.2 Tabular pharmacological information,
 - 2.6.3 Summary of pharmacokinetic information,
 - 2.6.4 Tabular pharmacokinetic information,
 - 2.6.5 Summary of toxicological information,
 - 2.6.6 Tabular toxicological information;
- 2.7 Summary of clinical investigation or documentation:
 - 2.7.1 Summary of biopharmaceutical investigations and relevant analytical methods
 - 2.7.2 Summary of clinical pharmacological investigations,
 - 2.7.3 Summary on clinical efficacy,
 - 2.7.4 Summary on clinical safety,
 - 2.7.5 Overview summary of individual studies.

Article 22

UNREVISED VERSION

Module 3 referred to in article 19 herein comprises information on medicinal product quality (pharmaceutical, chemical and biological information on medicinal products comprising an active substance of chemical or biological origin), namely:

3.1 Module 3 Table of contents;

3.2 Data:

3.2.S Active substance

3.2.S.1 General:

3.2.S.1.1 Classification

3.2.S.1.2 Structure,

3.2.S.1.3 Description,

3.2.S.2 Manufacturing:

3.2.S.2.1 Manufacturing site(s),

3.2.S.2.2 Description of manufacturing process and in-process control

3.2.S.2.3 Control of all starting materials,

3.2.S.2.4 Critical phase and intermediate controls,

3.2.S.2.5 Validation, that is, evaluation of the manufacturing process,

3.2.S.2.6 Development pharmaceuticals,

3.2.S.3 Description:

3.2.S.3.1 Description of structure and other properties,

3.2.S.3.2 Impurities,

3.2.S.4 Control of active substance:

3.2.S.4.1 Specifications,

3.2.S.4.2 Analytical methods,

3.2.S.4.3 Analytical method validation,

3.2.S.4.4 Batch analysis,

3.2.S.4.5 Verification of specification,

3.2.S.5 Reference standards or materials,

3.2.S.6 Container closure system,

3.2.S.7 Stability,

3.2.P Medicinal product/finished product (medicinal product)

3.2.P.1 Medicinal product description and composition,

3.2.P.2 Medicinal product development,

3.2.P.3 Manufacturing:

UNREVISED VERSION

- 3.2.P.3.1 Manufacturer,
 - 3.2.P.3.2 Manufacturing formula,
 - 3.2.P.3.3 Manufacturing process description and in-process control,
 - 3.2.P.3.4 Critical phase and intermediate controls,
 - 3.2.P.3.5 Manufacturing process validation, i.e. evaluation,
 - 3.2.P.4 Control of excipient:
 - 3.2.P.4.1 Specifications,
 - 3.2.P.4.2 Analytical methods,
 - 3.2.P.4.3 Analytical method validation,
 - 3.2.P.4.4 Verification of specification,
 - 3.2.P.4.5 Excipients obtained from human or animal source,
 - 3.2.P.4.6 New excipients,
 - 3.2.P.5 Control tests on the finished product (medicinal product):
 - 3.2.P.5.1 Specifications,
 - 3.2.P.5.2 Analytical methods,
 - 3.2.P.5.3 Analytical method validation,
 - 3.2.P.5.4 Batch analysis,
 - 3.2.P.5.5 Description of impurities,
 - 3.2.P.5.6 Verification of specification,
 - 3.2.P.6 Reference standards or materials,
 - 3.2.P.7 Container closure system,
 - 3.2.P.8 Stability,
 - 3.2.A Attachments
 - 3.2.A.1 Rooms and equipment,
 - 3.2.A.2 Medicinal product safety assessment relating to by-products (metabolites, degradation products),
 - 3.2.A.3 New excipients,
 - 3.2.P Regional information;
- 3.3. References.

Article 23

Module 4 referred to in article 19 herein comprises information on preclinical product investigation, namely:

- 4.1 Module 4 Table of Contents;
- 4.2 Investigation reports:

UNREVISED VERSION

4.2.1 Pharmacology

- 4.2.1.1 Primary pharmacodynamics,
- 4.2.1.2 Secondary pharmacodynamics,
- 4.2.1.3 Product safety pharmacology,
- 4.2.1.4 Pharmacodynamic interactions,

4.2.2 Pharmacokinetics

- 4.2.2.1 Analytical methods and validation reports,
- 4.2.2.2 Absorption,
- 4.2.2.3 Distribution,
- 4.2.2.4 Metabolism,
- 4.2.2.5 Excretion,
- 4.2.2.6 Pharmacokinetic interactions (non-clinical),
- 4.2.2.7 Other pharmacokinetic tests,

4.2.3 Toxicity

- 4.2.3.1 Toxicity after a single dose,
- 4.2.3.2 Toxicity after repeated administration,
- 4.2.3.3 Mutagenicity,
- 4.2.3.4 Carcinogenicity,
- 4.2.3.5 Reproductive toxicity,
- 4.2.3.6 Local tolerance,
- 4.2.3.7 Other toxicity studies;

4.3 References.

Article 24

Module 5 referred to in article 19 herein comprises information on clinical studies of a medicinal product, namely:

5.1 Module 5 Table of Contents;

5.2 Tabular overview of clinical studies conducted;

5.3 Clinical study reports:

- 5.3.1 Bioavailability/bioequivalence study reports,
- 5.3.2 Reports on pharmacokinetic studies of human biological material,
- 5.3.3 Reports on pharmacokinetic studies in humans,
- 5.3.4 Reports on pharmacodynamic studies in humans,
- 5.3.5 Reports on safety and efficacy studies,

UNREVISED VERSION

5.3.6 Post-marketing study reports,

5.3.7 Case reports and patient case report forms, if enclosed;

5.4 References.

Part II of a CTD dossier

Article 25

The CTD dossier Part II shall comprise separately processed and adapted information for the following categories of medicinal products:

- 1) Well-established medicinal use;
- 2) Essentially similar medicinal products;
- 3) Essentially similar medicinal products to be supported by additional information with regard to specific circumstances (e.g. different salt or ester of the same active substance);
- 4) Similar biological medicinal products;
- 5) Fixed combinations;
- 6) Inadequately documented medicinal products used in special cases only;
- 7) Medicinal products with mixed documentation in Modules 4 and 5.

The CTD dossier Part III

Article 26

The CTD dossier Part III shall comprise specific requirements with information depending on the origin of active substance, as well as requirements for information in respect of the use of medicinal product for:

- 1) Biological medicinal products;
- 2) Radiopharmaceutical medicinal products and precursors;
- 3) Homeopathic medicinal products;
- 4) Herbal medicinal products.

The CTD dossier Part IV

Article 27

UNREVISED VERSION

The CTD dossier Part IV shall include specific requirements with the information relating to medicinal products used in new therapeutic approaches (e.g. in gene therapy).

B. Documentation in the European dossier for medicinal products for human use

Article 28

The documentation contained in the European dossier for medicinal products for human use consists of four parts, namely:

Part 1. - Administrative data;

Part 2. – Pharmaceutical, chemical and biological documentation;

Part 3. – Pharmacological and toxicological documentation; and

Part 4. – Clinical documentation.

Part 1. of the European dossier documentation - Administrative documentation

Article 29

Part 1. of the European dossier type documentation referred to in article 28 herein relating to administrative documentation shall include:

- 1A: Administrative data;

- 1B: Data on Summary of Product Characteristics, labeling and patient information leaflet; and

- 1C: Specific expert reports for Parts 2, 3 and 4 for the European dossier documentation.

Article 30

1A: The administrative data referred to in article 29 herein shall include:

a) The application form properly completed;

b) Proof that the applicant meets all mandatory legal requirements or a reference to the data already submitted to the Agency (manufacturing license issued by the competent body, or Agency or representation agreement duly registered with the competent body);

v) The certificate of Good Manufacturing Practice (a *GMP* certificate) for the manufacturing site (an authenticated copy or the original certificate if required by the Agency), within three years of its issue;

UNREVISED VERSION

g) The list of countries where the medicinal product concerned has already been authorized (medicinal product trade name authorized, date of issue and authorization number), and/or in which the application has been submitted, rejected or in which authorization has been withdrawn and/or in which any such authorization has expired, as well as the name of the country of the first authorization;

d) Certificate of pharmaceutical product (*CPP*), that is, the proof that the product is actually marketed in the country of origin (e.g. a *FSC* certificate). If a medicinal product is manufactured by more than one manufacturing site or such manufacturing sites are located in more than one country, the manufacturer-applicant shall document interrelationship of such sites by submitting an appropriate interrelationship scheme to the Agency, to help explain the notion of the country of origin;

đ) Data on the samples submitted with data on the active substance standard(s) and, as needed, on standards of degradation products and impurities; the samples and standards referred herein shall meet the requirements of the two complete laboratory quality analyses;

e) Periodic safety update report (*PSUR*);

ž) Any additional data as required by the Agency and needed for the public health protection, that is, necessary for the assessment of the medicinal product risk/benefit ratio.

The manufacturer who is, pursuant to the Law, legally bound to harmonize the conditions of the medicinal product manufacturing with regulations adopted for the purpose of this Law enforcement, and with GMP guidelines, as well, may within a period of time specified by the Law submit the competent authority assessment of the fulfilment of conditions for the medicinal product concerned manufacturing in lieu of the certificate referred to in paragraph 1 clause v) of this article, provided that such assessment is issued within six months of the date of the submission of an application.

Article 31

Periodic safety update report (*PSUR*) referred to in article 30 clause e) herein shall include: introduction, worldwide regulatory status of a medicinal product, renewal of authorization, that is, renewal of authorization by the other countries' competent authorities, measures undertaken by the authorization holder for safety reasons, uses relevant to safety information, patient exposure case reports, clinical trials, data on the efficacy of medicinal products, latest results of the subsequent assessment of overall safety data, and conclusion.

Article 32

1B: Data on summary of product characteristics, labeling and patient information leaflet referred to in article 29 herein shall include:

UNREVISED VERSION

- a) Proposed summary of product characteristics (SmPC);
- b) Proposed patient information leaflet;
- v) Summary of product characteristics (SmPCs) authorized in other countries;
- g) Proposal of primary and secondary packaging (*mock-up*).

Article 33

Proposed summary of product characteristics referred to in article 32 clause 2 herein shall contain:

1. Name of the medicinal product, international non-proprietary name (INN);
2. Qualitative and quantitative composition;
3. Pharmaceutical form;
4. Clinical particulars:
 - 4.1. Therapeutic indications,
 - 4.2. Posology and method of administration,
 - 4.3. Contraindications,
 - 4.4. Special warnings and special precautions for use,
 - 4.5. Interaction with other medicinal products and other forms of interaction,
 - 4.6. Pregnancy and lactation,
 - 4.7. Effects on ability to drive and use machines,
 - 4.8. Undesirable effects,
 - 4.9. Overdose;
5. Pharmacological properties:
 - 5.1. Pharmacodynamic properties,
 - 5.2. Pharmacokinetic properties,
 - 5.3. Preclinical safety data;
6. Pharmaceutical particulars:
 - 6.1. List of excipients,
 - 6.2. Incompatibilities,
 - 6.3. Shelf-life,
 - 6.4. Special precautions for storage,
 - 6.5. Nature and contents of container,
 - 6.6. Special precautions for disposal of materials to be disposed of the after use of medicinal product;

UNREVISED VERSION

7. Marketing authorization holder;
8. Number of first marketing authorization/renewal of authorization;
9. Date of first authorization/renewal of authorization; and
10. Date of revision of the text.

The proposed summary of product characteristics referred to in paragraph 1 of this article the applicant substantiate by the original of the summary of product characteristics concerned in the English language as one of the officially used languages in the European Union that has been authorized in other countries in which the medicinal product concerned has been authorized.

The proposed summary of product characteristics referred to in paragraph 1 of this article shall conform to the scientific terminology used in the Republic of Serbia.

If the original text differs from the proposed summary of product characteristics, the applicant shall denote and explain any such differences.

Article 34

1.C: Specific expert reports for Parts 2, 3, and 4 of the documentation referred to in article 29 herein include:

- 1.C1. Expert report on the pharmaceutical, chemical and biological documentation;
- 1.C2. Expert report on the pharmaco-toxicological (preclinical) documentation;
- 1.C3. Expert report on the clinical documentation.

The expert reports referred to in paragraph 1 of this article shall be submitted to the Agency in the written or written and tabular form of the European dossier including quality, efficacy and safety data.

Part 2. of the European dossier documentation – Pharmaceutical, chemical and biological documentation

Article 35

Part 2. of the European dossier documentation referred to in article 28 herein relating to the pharmaceutical, chemical and biological documentation for medicinal products for human use shall include:

2A: Composition of the medicinal product:

- a) Composition of the medicinal product (unit formula);

UNREVISED VERSION

- b) Packaging and labeling (brief description);
- v) Clinical trial formulation;
- g) Medicinal product development.

2B: Description of the manufacturing process:

- a) Manufacturing formula (also including the batch size particulars);
- b) Manufacturing process;
- v) In-process control;
- g) Validation of the manufacturing process.

2C: Control of starting materials and packaging materials:

- 1. Active substance:
 - 1.1. Compendial active substance;
 - 1.1.1. Specification and routine tests;
 - 1.2. Active substance not described in a pharmacopeia;
 - 1.2.1. Specification and routine tests;
- 2. Excipients:
 - 2.1. Compendial excipients;
 - 2.1.1. Specification and routine tests;
 - 2.2. Excipients not described in a pharmacopeia;
 - 2.2.1. Specification and routine tests;
- 3. Packaging material (primary packaging):
 - 3.1. Specification and routine tests.

2Ca: Certificate and special precautions for the prevention of transmissible spongiform encephalopathy (TSE);

2D: Control tests on intermediate products (if appropriate);

2E: Control tests on the finished medicinal product:

- 1) Specification and routine tests;
- 2) Test methods;

UNREVISED VERSION

- 3) Scientific data;
- 4) Analytical method validation.

2F: Stability studies:

- 1) Stability tests on the active substance;
- 2) Stability tests on the finished product.

2G: Bioequivalence/Bioavailability:

The documentation on bioequivalence/bioavailability shall include data on the bioavailability/bioequivalence assessment, as required (abridged applications), related or submitted. A bioequivalence study shall be submitted to prove an essential similarity with the co-called reference medicinal product that shall be marketed in the Republic of Serbia, the European Union and/or other countries specifying the same requirements for the marketing authorization granting for at least six years.

If the bioavailability/bioequivalence data are required as the part of mixed application, a reference to that document shall be found in the European dossier Part IV.

2H: Environmental risk in case of medicinal products containing genetically modified organisms;

2Q: Miscellaneous;

2V: Virological documentation:

Virological documentation shall be submitted for all medicinal product of biological origin, that is, for each active substance of human or animal origin (e.g. blood products, animal cell extracts) or whose manufacturing includes such materials (e.g. biotechnological products obtained from human or animal cell cultures, immunopurified products, and alike), and for each excipient of human or animal origin (e.g. human serum albumin).

Virological documentation shall include:

- 1) Brief product description;
- 2) Starting materials and biological reagents used in the manufacturing;
- 3) Manufacturing process;
- 4) Validation of the manufacturing process;

UNREVISED VERSION

- 5) Virological control tests used in the course of the manufacturing process;
- 6) Pharmacovigilance data (monitoring of the virological safety);
- 7) Expert report.

Part 3 of the European dossier documentation – Pharmaco-toxicological documentation

Article 36

Part 3 of the European dossier documentation referred to in article 28 herein and relating to the pharmaco-toxicological documentation shall contain:

- 3 A – Study of toxicity after a single and repeated administration;
- 3 B – Reproductive function (fertility and common reproductive properties);
- 3 C – Embryo-fetal and perinatal toxicity;
- 3 D – Mutagenicity in *vitro*;
- 3 E – Carcinogenic potential;
- 3 F - Pharmacodynamics;
- 3 G - Pharmacokinetics;
- 3 H – Local tolerance (relative to the pharmaceutical product form and where appropriate);
- 3 I – Reference data;
- 3 Q – Other product data;
- 3 R – Environmental toxicity (particularly with vaccines).

Part 4 of the European dossier documentation – Clinical documentation

Article 37

Part 4 of the European dossier documentation referred to in Article 28 herein relating to the clinical documentation shall contain:

4A: Clinical pharmacology:

- 1) Pharmacodynamic data.

UNREVISED VERSION

The pharmacodynamic study results shall be submitted in the form of an aggregated report comprising the following:

1. Overview;
 2. Detailed study protocol;
 3. Study results including:
 - Study population;
 - Efficacy data;
 - Safety data;
 - Analysis of the results.
 4. Conclusions;
 5. References.
- 2) Pharmacokinetic data.

The pharmacokinetic study results shall be presented in the form of an aggregated report including the following:

1. Overview;
2. Detailed study protocol;
3. Results;
4. Conclusion;
5. References.

4B: Clinical experience shall consist of the following studies:

1. Clinical studies;
2. Post-marketing experiences (if available);
3. Published and unpublished clinical studies.

4I: Part referring to bibliographical applications.

4Q: Miscellaneous.

B. The European dossier documentation for medicinal product used solely in veterinary medicine

Article 38

The European dossier documentation for medicinal products used solely in veterinary medicine consists of four parts, namely:

Part 1 – Administrative documentation;

Part 2 – Documentation on the medicinal product quality (pharmaceutical, chemical and biological documentation);

Part 3 – Documentation on safety and residues testing (pharmaco-toxicological documentation and documentation on residues testing);

Part 4 – Documentation on efficacy (preclinical and clinical documentation).

The European dossier Part 1 documentation – Administrative documentation

Article 39

The Part 1 of the European dossier documentation referred to in article 38 herein and relating to the administrative documentation shall include:

- 1.A: Administrative data;
- 1.B: Summary of product characteristics, labeling and instructions for the user, and
- 1.C: Expert reports on the European dossier documentation.

Article 40

1.A: The administrative data referred to in article 39 herein shall include:

- a) The application form properly completed;
- b) Proof that the applicant meets all mandatory legal requirements or a reference to the data already submitted to the Agency (manufacturing license issued by the competent authority, or Agency or representation agreement duly registered with the competent body);

UNREVISED VERSION

v) The Certificate of Good Manufacturing Practices (a *GMP* certificate) for the manufacturing site (an authenticated copy or the original certificate if required by the Agency), within three years of its issue;

g) The list of countries where the medicinal product concerned has already been authorized (medicinal product trade name authorized, date of issue and authorization number), and/or in which the application has been submitted, refused or in which authorization has been withdrawn and/or in which any such authorization has expired, as well as the name of the country of the first authorization;

d) Certificate of pharmaceutical product (*CPP*), that is, the proof that the product is actually marketed in the country of origin (e.g. a *FSC* certificate). If a medicinal product is manufactured by more than one manufacturing site or such manufacturing sites are located in more than one country, the manufacturer-applicant shall document interrelationship of such sites by submitting an appropriate interrelationship scheme to the Agency, to help explain the notion of the country of origin;

đ) Data on the samples submitted with data on the active substance standard(s) and, as appropriate, data on standards of degradation products and impurities; the samples and standards referred herein shall meet requirements of the two complete laboratory quality analyses;

e) Periodic safety update report (*PSUR*);

ž) Any additional data as required by the Agency and needed for the health protection, that is, necessary for the assessment of the medicinal product risk/benefit ratio.

The manufacturer who is, pursuant to the Law, legally bound to harmonize the conditions of the medicinal product manufacturing with regulations adopted for the purpose of the Law enforcement, and with GMP guidelines, as well, may within a period of time specified by the Law, submit the competent authority assessment of the fulfilment of conditions for the medicinal product concerned manufacturing in lieu of the certificate referred to in paragraph 1 clause v) of this article, provided that such assessment is issued within six months of the date of the submission of his/her application.

Article 41

1.B: Summary of product characteristics, labeling and instructions for the user referred to in article 39 herein shall consist of:

1.B.1 Proposed summary of product characteristics (SmPC);

1.B.2 Proposed labeling and mock-ups of the packaging material and proposal of instructions for the user;

1.B.3 Summary of product characteristics (SmPCs) authorized in other countries.

Article 42

UNREVISED VERSION

1.C: Expert reports referred in article 39 herein shall include:

1.C.1 Introduction (general information);

1.C.2 Expert report relating to the type of application;

1.C.3 Expert reports:

1.C.3.1 Expert report on the product quality (pharmaceutical, chemical and biological);

1.C.3.2 Expert report on the product safety and residues (pharmacotoxicological report and report on residues);

1.C.3.3 Expert report on the product quality (preclinical and clinical).

The expert reports referred to in paragraph 1 of this article shall be submitted to the Agency in the written or written and tabular form of the European dossier including quality, efficacy and safety data on the medicinal product.

Article 43

The periodic safety update report for a medicinal product for the sole use in veterinary medicine (PSUR) referred to in article 40 paragraph 2 clause e) herein shall consist of the following: introduction, most recently authorized summary of product characteristics, measures undertaken by the competent authorities for safety reasons in the countries in which the subject product has been authorized or by the authorization holder, extent of the product availability, data on the authorization holder and data on the product, case reports, tabular presentation of the list of cases reported, overview of undesirable effects reported, published reports on undesirable effects, assessment of overall safety data and reported undesirable reactions in humans related to the use of a veterinary medicinal product, latest information, and conclusion.

Article 44

Proposal of the summary of product characteristics for a medicinal product for the sole use in veterinary medicine shall include:

1. Name of the medicinal product;

2. Qualitative and quantitative composition:

- Active substance (quantitative and qualitative formula per unit of volume, weight or dose unit),

- Excipient (the list of excipients and the quantity of substances known to be active);

3. Pharmaceutical form;

4. Pharmacological data:

UNREVISED VERSION

4.1. Pharmacodynamic properties,

4.2. Pharmacokinetic properties,

4.3. Data on the environmental impact;

5. Clinical data:

5.1. Target animal species (types and categories of animals to be treated with the medicinal product concerned)

5.2. Indications,

5.3. Contraindications,

5.4. Undesirable effects

5.5. Special warnings and precautions for use,

5.6. Use in pregnancy and lactation,

5.7. Interactions,

5.8. Posology and method of administration,

5.9. Overdose,

5.10. Special warning for each target species,

5.11. Withdrawal time,

5.12. Special warnings for persons administering veterinary medicinal product to animals;

6. Pharmaceutical particulars:

6.1. Incompatibilities,

6.2. Shelf-life,

6.3. Special precautions for storage,

6.4. Nature and contents of container,

6.5. Special precautions for the removal of unused medicinal product or medicinal product leftovers;

UNREVISED VERSION

7. Name and address of the authorization holder;
8. Restriction on the supply, distribution or use of the product concerned;
9. Authorization number;
10. Date of first authorization/renewal of authorization;
11. Date of revision of the text.

Part 2. of the European dossier documentation –Quality documentation

Article 45

The Part 2 of the European dossier documentation referred to in article 38 herein relating to the quality documentation on veterinary medicinal product, that is, pharmaceutical, chemical and biological documentation on the veterinary medicinal product concerned shall include:

2.A: Composition:

- 2.A.1 Composition,
- 2.A.2 Packaging – brief description,
- 2.A.3 Clinical trial formulation,
- 2.A.4 Product development;

2.B: Manufacturing process description:

- 2.B.1 Manufacturing formula,
- 2.B.2 Manufacturing process (with process flow-chart and in-process control),
- 2.B.3 Validation of the manufacturing process;

2.C: Control of starting materials and packaging material:

- 2.C.1 Active substance
 - 2.C.1.1 Specification and routine tests,
 - 2.C.1.1.1 Compendial active substance,
 - 2.C.1.1.2 Active substance not described in a pharmacopeia,
 - 2.C.1.2 Scientific data,
- 2.C.2 Excipients
 - 2.C.2.1 Specification and routine tests,
 - 2.C.2.1.1 Compendial excipients
 - 2.C.2.1.1 Excipients not described in a pharmacopeia,
 - 2.C.2.2 Scientific data (if new excipients are used),
- 2.C.3 Packaging material - primary packaging

UNREVISED VERSION

2.C.3.1 Specifications and routine tests,

2.C.3.2 Scientific data (material selection and analytical test results);

2.D: Special precautions for the prevention of animal transmissible spongiform encephalopathy (TSE);

2.E: Control tests on intermediate product (if appropriate);

2.F: Control tests on the finished product:

2.F.1 Specification and routine tests,

2.F.1.1 Test requirements and control tests,

2.F.1.2 Test methods,

2.F.2 Scientific data,

2.F.2.1 Analytical method validation,

2.F.2.2 Manufacturing batch testing;

2.G: Stability:

2.G.1 Stability tests on the active substance,

2.G.1 Stability tests on the finished;

2.H: Environmental risk assessment in case of products containing genetically modified organisms (GMO);

2Q: Miscellaneous.

Part 3 of the European dossier documentation – Documentation on the product safety and study of residues

Article 46

Part 3 of the European dossier documentation referred to in article 38 herein and relating to the documentation on the product safety and study of residues, that is to the pharmacotoxicological documentation and documentation on the study of residues shall include:

3.A Safety documentation (pharmaco-toxicological documentation):

3.A.1 Accurate identification of the active substance (classification, physicochemical properties, impurities, etc.)

3.A.2 Pharmacological studies

3.A.2.1 Pharmacodynamics,

3.A.2.2 Pharmacokinetics,

3.A.3 Toxicity studies

3.A.3.1 Toxicity after a single dose,

3.A.3.2 Toxicity after repeated administration,

3.A.3.3 Tolerance in target animal species,

UNREVISED VERSION

- 3.A.3.4 Reproductive toxicity and teratogenicity,
 - 3.A.3.4.1 Reproductive toxicity
 - 3.A.3.4.2 Embryo-fetal toxicity and teratogenic potential,
- 3.A.3.5 Mutagenicity,
- 3.A.3.6 Carcinogenicity,
- 3.A.4 Study of other effects
 - 3.A.4.1 Specific studies (immunotoxicity, endocrine function, hepatic and renal functions, impact on enzymes, neurotoxicity, hypersensitivity studies, cutaneous and ocular irritation, local tolerance, etc., as appropriate),
 - 3.A.4.2 Observations in humans,
 - 3.A.4.3 Microbial studies (impact on the human intestinal flora and organisms used in food processing),
 - 3.A.4.4 Study on metabolites, potentially hazardous impurities, other substances, and formulations,
- 3.A.5 User safety
- 3.A.6 Environmental risk assessment
- 3.B Documentation on residues:
 - 3.B.1 Exact product/active substance(s) identification (reference to 3.A.1)
 - 3.B.2 Study on residues
 - 3.B.2.1 Pharmacokinetics,
 - 3.B.2.2 Excretion of metabolite(s),
 - 3.B.2.3 Maximum residue limits (MRL),
 - 3.B.2.4 Withdrawal time
 - 3.B.3 Analytical methods to determine residues.

The applicant may be required by the Agency to supplement the data submitted referred to in article 40 herein.

Part 4 of the European dossier documentation – Safety documentation

Article 47

Part 4 of the European dossier documentation referred to in article 38 herein, relating to the documentation of the efficacy of a veterinary medicinal product, that is, to preclinical and clinical documentation shall include:

- 4.1 Preclinical documentation:
 - 4.1.A Clinical pharmacology,

UNREVISED VERSION

- 4.1.A.1 Pharmacodynamics,
- 4.1.A.2 Pharmacokinetics,
- 4.1.B Tolerance in target animal species,
- 4.1.C Resistance;
- 4.2 Clinical documentation.

Article 48

Documentation on bioequivalence/bioavailability shall include data on the biological availability assessment, or on bioequivalence, if appropriate.

If an abridged application is considered, the Part 3 of the European dossier documentation, relating to the safety and residues, and Part 4 relating to the product efficacy, may be substituted by the bioequivalence study to demonstrate essential similarity with the reference product, already marketed in the Republic of Serbia, the EU countries and/or in other countries specifying the same requirements for the marketing authorization granting for at least six years.

For the purpose of an abridged application, the documentation on residues including data on the study of residues and appropriate analytical methods shall be submitted within the Part 2 of the European dossier documentation, referred to in article 45 herein relating to the quality documentation (clause 2.Q: Miscellaneous).

If the data on bioavailability/bioequivalence are specified as an integral part of the mixed data application, the Part 4 of the European dossier documentation referred to in article 47 herein and the product safety documentation shall only hold the reference to the document.

G. The European dossier documentation on immunological medicinal product for the sole use in veterinary medicine.

Article 49

The European dossier type documentation for immunological veterinary medicinal products comprises of four parts, namely:

Part 1 – Administrative documentation;

Part 2 – Quality documentation – manufacturing and controls;

Part 3 – Safety documentation;

Part 4 – Efficacy documentation.

Part 1 of the European dossier documentation – Administrative documentation

UNREVISED VERSION

Article 50

The Part 1 of the European dossier documentation referred to in article 49 herein, relating to the administrative documentation shall include:

1.A Administrative particulars:

1.A.1 through 1.A.4 – The official application form,

1.A.5 The documentation to be submitted with the application (refer to part 1.A.5, referred to in article 40 paragraph 1 herein);

1.B Summary of product characteristics, labeling and user instruction:

1.B.1 Proposed summary of product characteristics (SmPC),

1.B.2 Proposed labeling and packaging mock-ups with the proposal of user instructions,

1.B.3 Summaries of product characteristics (*SmPCs*) authorized in other countries;

1.C Expert reports:

1.C.1 Introduction (general information),

1.C.2 Analytical Expert report,

1.C.3 Expert report on the product safety,

1.C.4 Expert report on the product efficacy.

Periodic safety update report (*PSUR*) for immunological medicinal product for the sole use in veterinary medicine shall include data referred to in article 43 herein.

Summary of product characteristics for immunological medicinal product for the sole use in veterinary medicine shall include data referred to in article 44 herein.

Part 2. – European Dossier - Quality documentation

Article 51

Part 2. European Dossier documentation referred to in Article 49 of The Rules relating to quality documentation – the manufacturing, control, i.e. physicochemical, biological and microbiological documentation shall include:

2.A Qualitative and quantitative composition:

2.A.1 Composition of the immunological medicinal product,

UNREVISED VERSION

- 2.A.2 Packaging – brief description,
- 2.A.3 Development pharmaceuticals,
- 2.A.4 Composition of batches for clinical study;
- 2.B Description of the method of preparation (including process flow diagram and process validation):
- 2.C Manufacturing and control of starting materials:
 - 2.C.1 Starting materials described in a pharmacopoeia,
 - 2.C.1.1 Title of the section of the European or national pharmacopoeia,
 - 2.C.1.2 Name, code etc. required for precise identification of the starting material,
 - 2.C.2 Starting materials not described in a pharmacopoeia
 - 2.C.2.1 Starting materials of biological origin
 - 2.C.2.2 Starting material of nonbiological origin,
 - 2.C.2.3 In-house media preparation
 - 2.C.2.4 Control and testing of in-house prepared media;
- 2.D Particular measures for the prevention of transmission of transmissible spongiform encephalopathy (TSE) of animals;
- 2.E In Process Control;
- 2.F Control of the finished product;
- 2.G Stability:
 - 2.G.1 Stability of the finished product,
 - 2.G.2 Stability of the reconstituted product;
- 2.H Environmental risk assessment for products containing, or consisting of genetically modified organisms (GMOs)
- 2.Q Other information.

Part 3 European Dossier – Safety data

Article 52

Part 3 European Dossier documentation referred to in Article 49 of The Rules relating to safety data shall include safety tests attached in the form of cumulative report having the following structure and contents:

UNREVISED VERSION

3.1 Introduction

3.2 Laboratory and field tests:

3.2.1 Name and reference number of the test,

3.2.2 General information and test objective,

3.2.3 Reference to the relevant section of the European pharmacopoeia,

3.2.4 Identification of subcontractors involved with testing,

3.2.5 Startup and end dates,

3.2.6 Summary,

3.2.7 Materials and methods,

3.2.8 Results,

3.2.9 Discussion,

3.2.10 Conclusions.

Part 4 European Dossier – Efficiency data

Article 53

Part 4 European Dossier documentation referred to in Article 49 of The Rules relating to efficiency data shall include efficiency test data attached in the form of cumulative report having the following structure and contents:

4.1 Introduction;

4.2. Laboratory and field tests:

4.2.1 Name and reference number of the study or experiment,

4.2.2 General information and test objective,

4.2.3 Reference to the relevant section of the European pharmacopoeia,

4.2.4 Identification of subcontractors involved with testing,

4.2.5 Startup and end dates,

UNREVISED VERSION

4.2.6 Summary,

4.2.7 Materials and methods,

4.2.8 Results,

4.2.9 Discussion,

4.2.10 Conclusions.

Article 54

Attached to the documentation associated with immunological medicinal products used exclusively in veterinary medicine, a list is submitted, as well as the copies of quoted papers that serve as the basis for the proposal of the literature data.

III VARIATIONS

Article 55

The authorisation holder is responsible for continual notification of the Agency of any new findings of quality, safety and efficiency of the marketed medicinal product and for submitting to the Agency the variation application, i.e. the request for variation approval based on the new findings of the medicinal product.

Article 56

Variations to authorisations can be:

- 1) Minor variations – Type I variations;
- 2) Major variations – Type II variations;
- 3) Variations requiring a new approval procedure.

Minor variations referred to in paragraph 1, clause 1) of this Article can be: Type IA and Type IB variations.

Article 57

The application or request for variation approval, considered to be a full application or request in the meaning of The Rules, shall include:

- 1) Cover letter of the authorisation holder;
- 2) Filled variation form;

UNREVISED VERSION

- 3) Documentation associated with variation containing sufficient data for its assessment;
- 4) Evidence of fees paid.

The application or request form referred to in paragraph 1 of this Article is attached to The Rules and comprises its integral part. (Form 2).

Article 58

The documentation referred to in Article 57 paragraph 1 clause 3) of The Rules is submitted in the format for which was granted the authorisation referred to in Article 17 of The Rules.

Notwithstanding the provision of paragraph 1 of this Article, the applicant may submit the documentation referred to in a different format but is strongly encouraged to reformat the originally submitted and approved document to adjust to the variation format.

Article 59

The Cover letter referred to in Article 57 paragraph 1, clause 1) of The Rules, shall include:

- 1) Logo, name and address of the authorisation holder;
- 2) Subject: Introduction of minor variation – Type IA or IB variation or Introduction of major variation – Type II variation;
- 3) Name of the medicinal product (proprietary name, INN or generic name, pharmaceutical form and strength). The name of the medicinal product shall be identical to that in the form and in the document;
- 4) Packaging of the medicinal product;
- 5) Name of the manufacturer;
- 6) Date and signature of the person responsible for variation application/request introduction.

Cover letter may refer to one variation only, except for consequential variations in which case the cover letter includes all variations.

Article 60

Full application/request for variation introduction includes all elements contained in the application for granting authorisation referred to in Article 3 of The Rules.

UNREVISED VERSION

The authorisation holder may, instead of re-submitting the documentation to the Agency, make reference to the previously submitted documentation for granting authorisation.

Article 61

The authorisation holder submits to the Agency the application/request for variation introduction.

The application/request for variation is assessed by the Agency for completeness within 30 days following the receipt of the application/request. The Agency informs the authorisation holder in writing of completeness/incompleteness of the application/request.

The authorisation holder referred to in paragraph 1 of this Article is responsible for notifying the Agency of the date of variation introduction.

Article 62

Following the positive assessment of the application/request completeness, the Agency shall subject the variation application/request to expert assessment.

In the process of the expert assessment of the application/request, the Agency may request the authorisation holder in writing to submit additional information or documentation required for the said expert assessment of variation application/request.

The term referred to in Article 61, paragraph 2 of The Rules is interrupted on the date of Agency request for additional information or documentation referred to in paragraph 2 of this Article to be resumed on the date of submittance of the said data by the authorisation holder.

If the authorisation holder fails to submit the variation application/request, the Agency shall refuse the application/request as incomplete.

Article 63

The Agency may refuse a Type IA variation application within 15 days from receiving a complete variation application.

The Agency may refuse a Type IB variation application within 30 days following the receipt of the request.

The Agency may refuse a Type II variation application or grant its introduction within 90 days following the receipt of the request.

If, within the term referred to in paragraphs 1 and 2 of this Article, the Agency does not notify the authorisation holder, the variations shall be considered approved.

UNREVISED VERSION

Article 64

The authorisation holder shall immediately notify the Agency of any emergency safety action undertaken by the authorisation holder relating to specific restrictions in medicinal product indications, change of dosage, additional contraindications and undesired events in the summary of product characteristics and patient information leaflet, or to other forms of restrictions, to avoid public health risks.

If the Agency has no objections to the effect of the emergency safety action referred to in paragraph 1 of this Article, the authorisation holder shall undertake the said action within 24 hours from Agency notification.

The authorisation holder shall submit to the Agency the filled form for the relating variation and the required documentation immediately after undertaking the emergency safety action referred to in paragraph 1 of this Article within 15 days at the latest.

Minor variations – Type IA and IB variations

Article 65

Minor variations of Type IA (hereinafter IA) and minor variations of Type IB (hereinafter IB) are associated with:

- 1) IA – Change in the name and/or address of the marketing authorisation holder provided the authorisation holder remains unchanged legal entity;
- 2) IB – change in the name of the medicinal product provided there is no doubt about the names of the marketed medicinal products or about the international nonproprietary name (INN);
- 3) IA – change of the name of the active substance provided the active substance remains unchanged;
- 4) IA – Change in the name and/or address of a manufacturer of the active substance where no Ph.Eur. or national pharmacopoeia Certificate of Suitability is available, and provided the manufacturing site remains unchanged;
- 5) IA – Change in the name and/or address of a manufacturer of the finished product provided the manufacturing site remains unchanged;
- 6) IA – change in ATC code of the medicinal products for human use or ATC code of the medicinal products for veterinary use after it has been assigned or after it has been changed by the WHO;
- 7) Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product:

UNREVISED VERSION

a) IA – change in Secondary packaging site for all types of pharmaceutical forms, and meeting the additional requirements referred to in subclauses 7.1 and 7.2 of this clause;

b) Change in primary packaging site:

- IA – solid pharmaceutical forms, and meeting the additional requirements referred to in the subclauses 7.1, 7.2, 7.3 and 7.5 of this clause;

- IB – semi-solid pharmaceutical forms, and meeting the additional requirements referred to in the subclauses 7.1, 7.2, 7.3 and 7.5 of this clause;

- IB – liquid pharmaceutical forms, and meeting the additional requirements referred to in the subclauses 7.1 to 7.5 of this clause;

c) IB – if the change is associated with the manufacturing site where other manufacturing processes are carried out, except batch release of medicinal products, and meeting the additional requirements referred to in the subclauses 7.1, 7.2, 7.4 and 7.5 of this clause;

The additional requirements in the meaning of this clause are:

7.1. The finding of the authorised inspection body that GMP requirements are met;

7.2. The approval by the authorised inspection body of manufacturing of the said pharmaceutical form on the specific manufacturing site;

7.3. The evidence that the medicinal product is not a sterile product;

7.4. The validation plan compliant with the validation protocol, demonstrated on at least three batches of the medicinal product;

7.5. The evidence that the medicinal product is not a biological products;

8) Change to batch release arrangements and quality control testing of the finished product:

a) IA – Replacement or addition of a site where batch control/testing of medicinal products takes place, and meeting the additional requirements referred to in the subclauses 8.2, 8.3 and 8.4 of this clause;

b) Replacement or addition of a manufacturer responsible for batch release:

- IA – the change does not include batch control/testing, and meeting the additional requirements referred to in the subclauses 8.1 and 8.2 of this clause;

- IA – the change includes batch control/testing, and meeting the additional requirements referred to in the subclauses 8.1. to 8.4 of this clause;

UNREVISED VERSION

The additional requirements in the meaning of this clause are:

8.1. The evidence that the manufacturer responsible for batch release is located on the territory of the Republic of Serbia, European Union or other countries specifying the same requirements for granting authorisation;

8.2. The approval by the authorised inspection body of the site for medicinal product manufacturing;

8.3. The evidence that the medicinal product is not a biological products;

8.4. The approval by the authorised inspection body of the change of the manufacturing site or of the site of laboratory control/testing of the medicinal product:

9) IA – Deletion of any manufacturing site including manufacturing site for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place;

10) IB – Minor change in the manufacturing process of the active substance provided that:

a) There are no changes in qualitative or quantitative impurity profile or physicochemical properties of the medicinal product;

b) The active ingredient is not a biological substance;

c) The route of synthesis remains unchanged as well as the intermediate products. If the medicinal products are of vegetable origin, their geographical location, vegetable substance manufacturing and method of manufacturing remain unchanged.

11) Change in batch size of active substance or intermediate:

a) IA – If the batch size is increased up to 10-fold compared to the original batch size approved at the grant of the authorisation, and meeting the additional requirements referred to in 11.1. to 11.4 of this clause 11;

b) IA – Downscaling, and meeting the additional requirements referred to in 11.1. to 11.5 of this clause 11;

c) IB – If the batch size is increased more than 10-fold compared to the original batch size approved at the grant of the authorisation, and meeting the additional requirements referred to in 11.1. to 11.4 of this clause 11.4.

The additional requirements in the meaning of this clause are:

UNREVISED VERSION

11.1. Change in the manufacturing process as a consequence of changed equipment resulting in changed batch size;

11.2. The results are available for at least two batches tested according to the specification of the proposed batch size;

11.3. The active substance is not a biological substance;

11.4. The change has no influence on the process repeatability;

11.5. The change results from no unexpected events during manufacture and is not associated with the product stability;

12) Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance:

a) IA and IB – Tightening of specification limits, and meeting the additional requirements referred to in subclauses 12.1 to 12.3 of this clause 12 for variation IA and additional requirements referred to in subclauses 11.2 and 11.3 for variation IB;

b) Addition of a new test parameter to the specification of:

- IB – An active substance, and meeting the additional requirements referred to in subclauses 12.2, 12.4 and 12.5 of this clause 12;

- IB – A starting material/intermediate/ reagent used in the manufacturing process of the active substance, and meeting the additional requirements referred to in subclauses 12.2 and 12.4 of this clause 12.

The additional requirements in the meaning of this clause are:

12.1. The change is not a consequence of the previously changed established specification limits approved in the process of granting authorisation or in the approval process of Type II variation;

12.2. The change is not a consequence of suddenly occurring events in the manufacturing process;

12.3. Any changes are within approved specification limits;

12.4. New test methods are not associated with the new nonstandard techniques or with the standard techniques applied in a new manner;

12.5. The active ingredient is not a biological substance;

UNREVISED VERSION

13) Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance:

a) IA – Minor change to an approved test procedure, and meeting the additional requirements referred to in subclauses 13.1, 13.2, 13.3. and 13.5 of this clause 13;

b) IB – Other changes to a test procedure, including replacement or addition of a test procedure, and meeting the additional requirements referred to in this clause, subclauses 13.2 to 13.5.

The additional requirements in the meaning of this clause are:

13.1. Analytical methods remain unchanged (e.g. column height is changed but not its type), with no new impurities to be identified;

13.2. Adequate (re)validation tests have been performed in accordance with the current guidance;

13.3. Validation results show that the new test methods are at least equivalent to previous procedures;

13.4. No new test method is associated with new nonstandard techniques or with the standard techniques applied in a new manner;

13.5. No active ingredient, starting materials, intermediate or reagent is a biological substances;

14) Change of the manufacturer of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance where no Ph. Eur. Certificate of Suitability is available:

a) IB – Change in site of the already approved manufacturer (replacement or addition), and meeting the additional requirements referred to in this clause, subclauses 14.1, 14.2 and 14.4;

b) IB – New manufacturer (replacement or addition), and meeting the additional requirements referred to in this clause, subclauses 14.1. to 14.4.

The additional requirements in the meaning of this clause are:

14.1. Specifications (including in-process control, test methods of all starting materials), manufacturing process (including batch size) and details of synthesis are identical to those in the granted authorisation;

14.2. For human or animal substances, the manufacturer shall not have a new supplier to be evaluated for virus and TSE safety in compliance to the current criteria;

UNREVISED VERSION

14.3. The current or the new manufacturer of an active substance does not implement the active substance Dossier, so-called, "Drug Master File";

14.4. The change does not refer to the medicinal product containing a biological active substance;

15) Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance:

a) IA – From a manufacturer currently approved, and meeting the additional requirements referred to in this clause, subclauses 15.1, 15.2 and 15.4;

b) From a new manufacturer (replacement or addition):

- IB – for sterile substances, and meeting the additional requirements referred to in this clause, subclauses 15.1. to 15.4;

- IA – for other substances, and meeting the additional requirements referred to in this clause, subclauses 15.1. to 15.4;

c) IB – when the certificate relates to a substance in veterinary medicinal product for use in animal species susceptible to TSE (transferrable spongiform encephalopathy), and meeting the additional requirements referred to in this clause, subclauses 15.1 to 15.4.

The additional requirements in the meaning of this clause are:

15.1. The release specification of the medicinal product and shelf life remain unchanged;

15.2. The additional specifications (those in the European Pharmacopoeia or the national pharmacopoeia) for impurities and other medicinal product requirements (e.g. particle size, polymorphism) remain unchanged;

15.3. The active ingredient shall be analysed before use if the certificate of compliance with EP monographs does not include the retest period or the evidence of the retest period is not submitted;

15.4. The manufacturing process of an active substance or starting material/reagent/intermediate does not involve human or animal substances requiring the virus safety evaluation;

16) Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance for a currently approved manufacturer and currently approved manufacturing process:

UNREVISED VERSION

a) IB – Substance in veterinary medicinal product for use in animal species susceptible to TSE;

b) IA – other substances;

17) Change in:

a) IB – The re-test period of the active substance, and meeting the requirements of clause 17. (IB subclauses 17.1. to 17.3);

b) IB – The storage conditions for the active substance, and meeting the requirements of this clause, subclauses 17.1 and 17.2.

The additional requirements in the meaning of this clause are:

17.1. Stability tests are performed in compliance with the approved stability protocol;

17.2. The changes result from no unexpected events in the manufacturing process and are not associated with product stability;

17.3. The active substance is not a biological substance;

18) Replacement of an excipient with a comparable excipient - IB.

The additional requirements in the meaning of this clause are:

18.1. Functional characteristics of excipients remain unchanged;

18.2. Active substance dissolution and release profiles tested on at least two pilot batches of a new product are comparable to those established for the previous product;

18.3. New excipients do not involve human- or animal-origin substances requiring virus safety evaluation. The risk associated with the excipients of veterinary medicinal products intended for use in animal species susceptible to TSE is evaluated by the Agency;

18.4. The medicinal product contains no biological active substances;

18.5. There is an ongoing stability study of at least two pilot batches or two industrial batches and the applicant has the evidence of a satisfactory three-month stability profile and agrees to finish the study and to immediately notify the Agency of any OOS results obtained for the product at the end of shelf life;

19) Change in specification of an excipient:

UNREVISED VERSION

a) IA and IB – Tightening of specification limits, and meeting the additional requirements referred to in this clause, subclauses 19.1. to 19.3. for IA, and meeting the additional requirements referred to in this clause, subclauses 19.2 and 19.3. for IB;

b) IB – Addition of a new test parameter to the specification, and meeting the additional requirements referred to in this clause, subclauses 19.2, 19.4. and 19.5.

The additional requirements in the meaning of this clause are:

19.1. The change does not result from the previous evaluation of the specification limits approved in the process of granting authorisation or in the process of variation type II approval.;

19.2. The change is the result of no unexpected events in production;

19.3. The changes are already within the approved specification limits;

19.4. New test methods are not associated with the new nonstandard techniques or with the standard techniques applied in a new manner;

19.5. The change is not associated to vaccine adjuvants or biological excipients.

20) Change in test procedure for an excipient:

a) IA – Minor change to an approved test procedure, and meeting the additional requirements referred to in this clause, subclauses 20.1, 20.2, 20.3 and 20.5;

b) IB – Minor change to an approved test procedure for a biological excipient, and meeting the additional requirements referred to in this clause, subclauses 20.1. to 20.3;

c) IB – Other changes to a test procedure, including replacement of an approved test procedure by a new test procedure, and meeting the additional requirements referred to in this clause, subclauses 20.2. to 20.5.

The additional requirements in the meaning of this clause are:

20.1. Analytical methods remain unchanged with no new impurities to be identified;

20.2. Appropriate (re)validations have been performed according to current guidance;

20.3. Validation result show that the new test procedures are at least equivalent to the previous procedures;

20.4. No new test method is associated with new nonstandard techniques or with the standard techniques applied in a new manner;

UNREVISED VERSION

20.5. The excipient is not a biological substance.

21) Submission of a new or updated Ph. Eur. Certificate of Suitability for an excipient:

a) IA – From a manufacturer currently approved, and meeting the additional requirements referred to in this clause, subclauses 21.1. to 21.3;

b) From a new manufacturer (replacement or addition):

- IB –Sterile substance, and meeting the additional requirements referred to in this clause, subclauses 21.1. to 21.3;

- IA – Other substances, and meeting the additional requirements referred to in this clause, subclauses 21.1. to 21.3.

c) IB – Substance in veterinary medicinal product for use in animal species susceptible to TSE, and meeting the additional requirements referred to in this clause, subclauses 21.1. to 21.3.

The additional requirements in the meaning of this clause are:

21.1. Specification for medicinal product release and its shelf life remain unchanged;

21.2. Additional specifications (those in the European Pharmacopoeia or the national pharmacopoeia) for impurities and other medicinal product requirements (e.g. particle size, polymorphism) remain unchanged, if applicable ;

21.3. The manufacturing process of excipients does not involve human- or animal-origin substances for which the evaluation of virus safety data is required;

22) Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an excipient:

a) IA - From a manufacturer currently approved or a new manufacturer (replacement or addition);

b) IB - Excipient in veterinary medicinal product for use in animal species susceptible to TSE;

23) Change in a TSE-hazardous source of an excipient or reagent used in a vegetable or synthetic material:

a) IB – Excipient or reagent used in the manufacture of biological active substance or a finished product containing a biological active substance;

UNREVISED VERSION

b) IA – Other cases provided the release specification of an excipient or that of a medicinal product remains unchanged as well as the shelf life of the medicinal product.

24) Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the Dossier), provided there are no changes in the qualitative or quantitative impurity profile or of the physicochemical properties of the medicinal product and that the excipient is not a biological substance - IB;

25) Change to comply with Ph. Eur. or with the national pharmacopoeia;

a) Change to specification(s) of a former non-European pharmacopoeial substance to comply with Ph. Eur. or with the national pharmacopoeia:

- IB – Active substance, and meeting the additional requirements referred to in this clause, subclauses 25.1. and 25.2;

- IB – excipient, and meeting the additional requirements referred to in this clause, subclauses 25.1. and 25.2.

b) Change to comply with an update of the relevant monograph of the Ph. Eur or national pharmacopoeia:

- IA - Active substance, and meeting the additional requirements referred to in this clause 25.1. and 25.2;

- IA – excipient, and meeting the additional requirements referred to in this clause, subclauses 25.1. and 25.2.

The additional requirements in the meaning of this clause are:

25.1. The change is made for the purpose of compliance with the recent edition of the Ph. Eur. or the national pharmacopoeia;

25.2. The product-specific specification remains unchanged (additional to compendial requirements), if appropriate.

26) Change in the specifications of the immediate packaging of the finished product:

a) IA and IB - Tightening of specification limits, and meeting the additional requirements referred to in subclauses 26.1. to 26.3. for IA, and meeting the additional requirements referred to in subclauses 26.2. and 26.3. for IB;

b) IB – Addition of a new test parameter to the specification, and meeting the additional requirements referred to in subclauses 26.2 and 26.4.

The additional requirements in the meaning of this clause are:

UNREVISED VERSION

26.1. The change does not result from the obligation arising out of the previous specification limit assessments approved within the procedure for granting authorisation or within the procedure for the approval of type II variation;

26.2. The change results from no unexpected production events;

26.3. The changes are within the approved specification limits;

26.4. New test methods are not associated with the new nonstandard techniques or with the standard techniques applied in a new manner;

27) Change to a test procedure of the immediate packaging of the finished product:

a) IA – Minor change to an approved test procedure, and meeting the additional requirements referred to in subclauses 27.1. to 27.3;

b) IB – Other changes to a test procedure, including replacement or addition of a test procedure, and meeting the additional requirements referred to in subclauses 27.2. to 27.4.

The additional requirements in the meaning of this clause are:

27.1. Analytical methods remain unchanged;

27.2. The relevant (re)validations are carried out in compliance with the current guidance;

27.3. Validation results show that the new test procedures are at least equivalent to the previous ones;

27.4. No new test method is associated with the new nonstandard techniques or with the standard techniques applied in a new manner;

28) IA – Change in any part of the (primary) packaging material not in contact with the finished product formulation provided the change is not associated with the main part of the packaging material affecting delivery, application and safety of the medicinal product or its stability;

29) Change in the qualitative and/or quantitative composition of the immediate packaging material:

a) IB – Semi-solid and liquid pharmaceutical forms, and meeting the additional requirements referred to in subclauses 29.1. to 29.4;

b) IA and IB – All other pharmaceutical forms, and meeting the additional requirements referred to in subclauses 29.1. to 29.4. for IA, and meeting the additional requirements referred to in subclauses 29.1. 29.3. 29.4 for IB.

UNREVISED VERSION

The additional requirements in the meaning of this clause are:

29.1. The product is not a biological or sterile product;

29.2. The change is associated with the identical type of the packaging or packaging material (e.g. blister remains blister);

29.3. The proposed packaging material shall be at least equivalent to the approved packaging material in terms of its relevant characteristics;

29.4. There is an ongoing stability study of at least two pilot batches or two industrial batches and the applicant has the evidence of a satisfactory three-month stability profile and agrees to finish the study and to immediately notify the Agency of any out-of-specification (OOS) results obtained for the product at the end of shelf life.

30) Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the Dossier), spacer devices for metered dose inhalers are excluded:

a) IA – Deletion of a supplier, and meeting the additional requirements referred to of subclause 30.1;

b) IB – Replacement or addition of a supplier, and meeting the additional requirements referred to in subclauses 30.1. to 30.4.

The additional requirements in the meaning of this clause are:

30.1. No constituent part of the packaging or the medical device is deleted;

30.2. Qualitative and quantitative composition of parts of the packaging or of the medical device remains unchanged;

30.3. Quality control specifications and methods remain at least equivalent;

30.4. For sterile products, the sterilisation methods and conditions remain unchanged;

31) Change to in-process tests or limits applied during the manufacture of the product:

a) IA and IB – Tightening of in-process limits, and meeting the additional requirements referred to in subclauses 31.1 to 31.3. for variation IA, and additional requirements in subclauses 31.2. and 31.3. for variation IB.

b) IB – Addition of new tests and limits, and meeting the additional requirements referred to in subclauses 31.2. and 31.4.

The additional requirements in the meaning of this clause are:

UNREVISED VERSION

31.1. The change does not result from the obligation of the previous assessment of specification limits approved within the process of granting authorisation in the process of variation type II approval.;

31.2. The change results from no unexpected production events;

31.3. The changes are within the approved specification limits;

31.4. New test methods are not associated with the new nonstandard techniques or with the standard techniques applied in a new manner;

32) Change in batch size of the finished product:

a) IA – Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation, and meeting the additional requirements referred to in 32.1. to 32.5;

b) IA – Downscaling down to 10-fold, and meeting the additional requirements referred to in 32.1. to 32.6;

c) IB – Other situations, and meeting the additional requirements referred to in 32.1. to 32.7.

The additional requirements in the meaning of this clause are:

32.1. The change does not affect the product reproducibility or consistency;

32.2. The change applies only to oral pharmaceutical forms and to nonsterile liquid pharmaceutical forms;

32.3. Any changes to the manufacturing or control method are those resulting from batch size change;

32.4. A validation plan is available or validation has been carried out that is based on the validation protocol with at least three proposed batch sizes and in compliance with the current guidance;

32.5. Not applicable to the medicinal product containing a biological active substance;

32.6. The change results from no unexpected changes as a consequence of unexpected manufacturing events or those associated with the product stability;

32.7. There is an ongoing stability study of at least two pilot batches or two industrial batches and the applicant has the evidence of a satisfactory three-month stability profile and agrees to finish the study and to immediately notify the Agency of any OOS results obtained for the product at the end of shelf life;

UNREVISED VERSION

33) IB – Minor change in the manufacture of the finished product.

The additional requirements in the meaning of this clause are:

33.1. Manufacturing principle remains unchanged;

33.2. New procedures lead to identical product in terms of all aspects of quality, safety and efficiency;

33.3. Medicinal product does not contain a biological active substance;

33.4. For sterilisation procedure, the change is associated only with the standard compendial cycles;

33.5. There is an ongoing stability study of at least two pilot batches or two industrial batches and the applicant has the evidence of a satisfactory three-month stability profile and agrees to finish the study and to immediately notify the Agency of any OOS results obtained for the product at the end of shelf life;

34) Change in the colouring system or the flavouring system currently used in the finished product:

a) Reduction or deletion of one or more components of the:

- IA – Colouring system, and meeting the additional requirements referred to in 34.1. to 34.4. and 34.7;

- IA – Flavouring system, and meeting the additional requirements referred to in subclauses 34.1. to 34.4. and 34.7;

b) Increase, addition or replacement of one or more components of:

- IB - Colouring system, and meeting the additional requirements referred to in subclauses 34.1. to 34.7;

- IB - Flavouring system, and meeting the additional requirements referred to in subclauses 34.1. to 34.7;

The additional requirements in the meaning of this clause are:

34.1. There are no changes of the functional characteristics of the pharmaceutical form (rate of active ingredient dissolution and release, disintegration time);

34.2. Any minor adjustments of the excipient representing the major part of the product intended to maintain the specified weight of the pharmaceutical form;

UNREVISED VERSION

34.3. Medicinal product specifications are updated only in terms of appearance, odour and flavour and, if appropriate, in terms of addition or deletion of identification test ;

34.4. There is an ongoing stability study (real-time study and study under other conditions – accelerated ageing) on at least two pilot batches or two industrial batches and the applicant has the evidence of a satisfactory three-month stability profile and agrees to finish the study and to immediately notify the Agency of any OOS results obtained for the product at the end of shelf life;

34.5. Any new components shall comply to the colouring or flavouring systems;

34.6. The new components do not involve a human- or animal-origin material requiring the assessment of virus safety;

34.7. Biological substances in veterinary medicinal products for oral use in which the colouring or flavouring systems are important for use with target animal species are excluded;

35) Change in coating weight of tablets or change in weight of capsule shells:

a) IA – Immediate release oral pharmaceutical forms, and meeting the additional requirements referred to in subclauses 35.1, 35.3. and 5.4;

b) IB – Gastro-resistant, modified or prolonged release pharmaceutical forms, and meeting the additional requirements referred to in subclauses 35.1. to 35.4.

The additional requirements in the meaning of this clause are:

35.1. Dissolution and release rates of the active ingredient have been evaluated on at least two pilot batches and the obtained results have shown to be comparable with the previous ones. In vegetable-origin medicinal products where the active ingredient dissolution and release rates cannot be determined, disintegration time shall be comparable;

35.2. Film coating agent does not have an important role in the active ingredient release mechanism;

35.3. Finished product specification is updated, as required, in terms of weight and dimensions;

35.4. There is an ongoing stability study (real-time study and study under other conditions – accelerated ageing) of at least two pilot batches or two industrial batches and the applicant has the evidence of a satisfactory three-month stability profile and agrees to finish the study and to immediately notify the Agency of any OOS results obtained for the product at the end of shelf life;

UNREVISED VERSION

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

a) IB – Sterile pharmaceutical forms and biological medicinal products, and meeting the additional requirements referred to in subclauses 36.1. to 36.3;

b) IA – Other pharmaceutical forms, and meeting the additional requirements referred to in subclauses 36.1 to 36.3.

The additional requirements in the meaning of this clause are:

36.1. There are no changes to the qualitative or quantitative composition of the container;

36.2. The change refers to the main part of the packaging component affecting delivery, use, safety or efficiency of the medicinal product;

36.3. If the change refers to the free area of the container or to the area and volume ratio, there are ongoing stability studies on at least two pilot batches (three batches of the biological medicinal products) or on the industrial batches being manufactured and the applicant has the evidence of a satisfactory three-month stability profile (six months for biological medicinal products) and agrees to finish the studies and to immediately notify the Agency of any OOS results obtained for the products at the end of shelf life;

37) Change in the specification of the finished product:

a) IA and IB - Tightening of specification limits, and meeting the additional requirements referred to in subclauses 37.1. to 37.3. of this clause for variation IA and additional requirements referred to in subclauses 37.2. and 37.3. for variation IB;

b) IB – Addition of a new test parameter, and meeting the additional requirements referred to in subclauses 37.2, 37.4. and 37.5.

The additional requirements in the meaning of this clause are:

37.1. The change does not result from the previous evaluation of the specification limits approved in the process of granting authorisation or in the process of variation type II approval.;

37.2. The change results from no unexpected events in production;

37.3. The changes are within the specification limits;

37.4. New test methods are not associated with the new nonstandard techniques or with the standard techniques applied in a new manner;

37.5. Test procedures are not associated with the biological active substance or a biological excipient in the medicinal products;

UNREVISED VERSION

38) Change in test procedure of the finished product:

a) IA – Minor change to an approved test procedure, and meeting the additional requirements referred to in subclauses 38.1. to 38.5;

b) IB - Minor change to an approved test procedure for biological active substance or biological excipient, and meeting the additional requirements referred to in subclauses 38.1. to 38.4;

c) IB – Other changes to a test procedure, including replacement or addition of a test procedure, and meeting the additional requirements referred to in subclauses 38.2. to 38.5.

The additional requirements in the meaning of this clause are:

38.1. Analytical methods remain unchanged;

38.2. Relevant (re)validations are performed in compliance with the current guidance;

38.3. Validation results show that the new test procedures are at least equivalent to the previous ones;

38.4. No new test method is associated with the new nonstandard techniques or with the standard techniques applied in a new manner;

38.5. Test procedures are not associated with a biological active substance or a biological excipient in the medicinal product;

39) IA – Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking.

The additional requirements in the meaning of this clause are:

39.1. The release specification of the finished product and the specifications associated with the expiry date (other than appearance) remain unchanged;

39.2. The new product marking ink shall be in compliance with the current regulations;

40) Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean weight:

a) IB – Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets, and meeting the additional requirements referred to in subclauses 40.1. and 40.2;

UNREVISED VERSION

b) IA – All other tablets, capsules, suppositories and pessaries, and meeting the additional requirements referred to in subclauses 40.1. and 40.2.

The additional requirements in the meaning of this clause are:

40.1. Dissolution and release rates of the active substance after the product has been reformulated are comparable to those of the previous formulation. In vegetable-origin medicinal products where the active ingredient dissolution and release rates cannot be determined, disintegration time shall be comparable;

40.2. The release specification of the finished product and the specification associated with the expiry date (other than dimensions) remain unchanged;

41) Change in pack size of the finished product:

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

- IA – Change within the range of the currently approved pack sizes, and meeting the additional requirements referred to in subclauses 41.1. and 41.2.;

- IB – Change outside the range of the currently approved pack sizes, and meeting the additional requirements referred to in subclauses 41.1. and 41.2.;

b) IB – Change in the fill-weight/fill volume of non-parenteral multi-dose products, and meeting the additional requirements referred to in subclauses 41.1. and 41.2.

The additional requirements in the meaning of this clause are:

41.1. New pack sizes shall be compliant with the dosage and duration of treatment proposed in the SmPC of the medicinal product;

41.2 Primary packaging components remain unchanged;

42) Change in:

a) the shelf life of the finished product:

- IB – As packaged for sale, and meeting the additional requirements referred to in subclauses 42.1. to 42.3.;

- IB – After first opening, and meeting the additional requirements referred to in subclauses 42.1. and 42.2.;

- IB – After dilution or reconstitution, and meeting the additional requirements referred to in subclauses 42.1. and 42.2.;

UNREVISED VERSION

b) IB – The storage conditions of the finished product or the diluted/reconstituted product, and meeting the additional requirements referred to in subclauses 42.1, 42.2 and 42.4.

The additional requirements in the meaning of this clause are:

42.1. Stability studies have been performed according to the approved protocols. The studies shall demonstrate that the approved specifications have been fulfilled;

42.2. The change results from no unexpected events in production or unacceptable stability of the product;

42.3. Shelf life is not longer than five years;

42.4. The product is not a biological medicinal product;

43) Addition, replacement or deletion of a metering or administration device not being an integrated part of the primary packaging (spacer devices for metered dose inhalers are excluded):

a) Medicinal products for human use:

- IA – Addition or replacement, and meeting the additional requirements referred to in subclauses 43.1. and 43.2;

- IB – Deletion, and meeting the additional requirements referred to in subclause 43.3;

b) IB - Veterinary medicinal products, and meeting the additional requirements referred to in subclauses 43.1. and 43.2.

The additional requirements in the meaning of this clause are:

43.1. The proposed metering/administration device shall measure/administer the required dose of the product accurately and in compliance with the specified dosing of the medicinal product; the results of these test shall be available;

43.2. A new medical device shall be compatible with the medicinal product;

43.3. Accurate dosing of the medicinal product shall be still possible;

44) Change in specification of a metering device or administration device for veterinary medicinal products:

a) IA and IB - Tightening of specification limits, and meeting the additional requirements referred to in subclauses 44.1 to 44.3 for variation IA, and additional requirements in subclauses 44.2. and 44.3. for variation IB;

UNREVISED VERSION

b) IB – Addition of new test parameters, and meeting the additional requirements referred to in subclauses 44.2. and 44.4.

The additional requirements in the meaning of this clause are:

44.1. The change does not result from the previous evaluation of the specification limits approved in the process of granting authorisation or in the process of variation type II approval;

44.2. The change does not result from unexpected events in production;

44.3. The changes are within the approved specification limits;

44.4. New test methods are not associated with the new nonstandard techniques or with the standard techniques applied in a new manner.

45) Change in test procedure of a metering or administration device for veterinary medicinal products:

a) IA – Minor change to an approved test procedure, and meeting the additional requirements referred to in subclauses 45.1. to 45.3;

b) IB – Other changes to a test procedure, including replacement of approved test procedure by new test procedure, and meeting the additional requirements referred to in subclauses. 45.2. to 45.4.

The additional requirements in the meaning of this clause are:

45.1. It has been demonstrated that that the new or updated test procedure is at least equivalent to the approved one;

45.2. Relevant (re)validations are performed in compliance with the current guidance;

45.3. The results of the method validation demonstrate that the new test procedure is at least equivalent to the approved one;

45.4. New test methods are not associated with the new nonstandard techniques or with the standard techniques applied in a new manner;

46) Change in the Summary of Product Characteristics of an essentially similar product following a reference summary of product characteristics for an original medicinal product used for demonstrating the essential similarity.

Variations in the paragraph 1 of this Article, ordinal numbers 1 to 46, are considered main changes in the meaning of this Rules.

UNREVISED VERSION

The variations occurring as a consequence of the introduction of the main change in paragraph 2 of this Article are considered, in the meaning of this Rules, consequential variations which shall be submitted to the Agency together with the main variation.

Major variations or Type II variations

Article 66

A Type I variation processed using the procedure applicable to Type II variation refers to an individual variation of immunological medicinal products, medicinal products obtained from blood and plasma and biotechnological medicinal products.

Article 67

A Type II variation is a variation included neither in type I variation nor in the variation requiring a new drug application.

A Type II variation is any change to the documentation having already been submitted by the applicant for authorisation granting that is not a Type I variation.

A Type II variation refers to any amendments to administrative data, pharmaceutical-chemical and biological part of the Dossier, or changes to the clinical data of the Dossier, leading to the changes to the summary of product characteristics, labelling and packaging of the medicinal product. The changes are briefly presented in Form 2 attached to this Rules as its integral part.

Variations requiring a new authorisation application

Article 68

The authorisation holder submits to the Agency a new variation application for:

- 1) The active substance;
- 2) Strength, pharmaceutical form and route of administration.

The new application in paragraph 1 of this Article and in the meaning of this Rules is considered to be the extension application.

Article 69

Change to the active substance:

- 1) Addition of an active substance including vaccine antigens
- 2) Deletion of an active substance including vaccine antigens;

UNREVISED VERSION

- 3) Change in the quantity of an active substance;
- 4) Additional form of an active substance (additional form of a salt, ester or other derivatives with the same therapeutic moiety);
- 5) Replacement of an active substance by an isomer or a complex or replacement of a racemate by one enantiomer;
- 6) Replacement of a biological substance or a biotechnological product by other substance/product having a different molecular structure; change to a vector used for obtaining the biotechnological product or change to a cell bank ;
- 7) Additional ligand or a binding system in a radiopharmaceutical product.

Article 70

Changes in strength, pharmaceutical form and route of administration:

- 1) Change in bioavailability;
- 2) Change in pharmacokinetic;
- 3) Additional strength;
- 4) Change in or addition of a pharmaceutical form;
- 5) Addition of a route of administration.

Article 71

Change to the authorisation, in the meaning of this Rules, is considered to be authorisation transfer from one authorisation holder to the new authorisation holder.

Within 30 days from the receipt of the request for authorisation change – authorisation transfer the Agency makes a decision in writing of the approval or refusal of the application for authorisation transfer.

The form for change to authorisation – authorisation transfer is attached to this Rules as its integrated part (Form 3).

IV RENEWAL APPLICATION

Article 72

The authorisation holder shall submit a renewal application to the Agency within 90 days before its expiry.

UNREVISED VERSION

Article 73

The renewal application in Article 72 of this Rules shall include:

request in the meaning of The Rules, shall include:

- 1) Cover letter for granting authorisation;
- 2) Filled form for granting authorisation;
- 3) Documentation on the medicinal product as specified by this Rules;
- 4) Evidence of fees paid.

With the application for granting authorisation the applicant submits to the Agency the samples of the medicinal product in the quantity sufficient for double laboratory testing.

The application form in paragraph 1 clause 2) of this Article is submitted for each pharmaceutical form, strength and packaging.

The application form in paragraph 1 clause 2) of this Article is attached as hard copy to this Rules and makes its integrated part (Form 4).

Article 74

Cover letter in Article 73, paragraph 1 clause 1) of this Rules shall include:

- 1) Logo, name and address of the applicant;
- 2) Subject of the application;
- 3) Name of the medicinal product (proprietary name, INN or generic name, pharmaceutical form and strength) with the required clarifications in the Dossier and form;
- 4) Packaging of the medicinal product;
- 5) Name of the manufacturer;
- 6) Date and number of the issued authorisation;
- 7) Date and signature of the person responsible for obtaining authorisation.

Cover letter in paragraph 1 of this article may be associated with multiple applications for granting and uthorisation.

UNREVISED VERSION

Article 75

Medicinal product documentation referred to in Article 73, paragraph 1 clause 3) of this Rules shall include:

- 1) Updated administrative data;
- 2) Updated summary of product characteristics incorporating the most recent changes to the SmPC of the medicinal product;
- 3) Proposed patient/customer information leaflet;
- 4) Proposed mock-up and design of the secondary packaging;
- 5) The most recent periodic safety update report;
- 6) TSE certificate.

Article 76

The medicinal product documentation referred to in Article 75 of this Rules is submitted to the Agency in writing in the language in official use in the Republic of Serbia.

The electronic version of the documentation referred to in paragraph 1 of this Article may be submitted to the Agency.

The documentation referred to in paragraph 1 of this Article may be submitted in the English language which is one of languages in official use in the EU, excluding the summary of product characteristics, proposed patient/customer information leaflet and the proposed primary and secondary packaging which are submitted to the Agency only in the language and using the script in official use in the Republic of Serbia.

The photocopy of the original documentation referred to in paragraph 1 of this Article may be submitted unless this Rules specifies that original has to be submitted.

If the applicant submits the documentation referred to in paragraph 1 of this Article as an electronic copy, the applicant shall sign a statement testifying that he shall, on Agency request, submit a hard copy of the documentation within 30 days from submitting its electronic version.

If the applicant submits a photocopy of the original documentation referred to in paragraph 1 of this Article, he shall make a statement to testify that the photocopy is identical to the original.

Subject to the Agency request, two copies at the most of the documentation referred to in paragraph 1 of this Article shall be submitted.

UNREVISED VERSION

Article 77

The Agency takes into consideration only a full application containing all data referred to in Article 73 of this Rules.

The Agency shall, within 30 days from the introduction of application, assess the completeness of the application and inform the applicant in writing of its finding in terms of application completeness or incompleteness.

If the application is incomplete, the Agency requests of the applicant to submit the specified information within 30 days from the receipt of the notification described in paragraph 2 of this Article.

If the applicant fails to submit the required information in the term specified in paragraph 3 of this Article, the Agency shall refuse the renewal application as incomplete.

Article 78

If the application is complete, the 90-day term for issuing renewal authorisation starts.

The term in paragraph 1 of this Article starts on the day of the applicant's receipt the Agency notification of completeness.

Article 79

After the assessment of completeness, the Agency undertakes the expert evaluation of the medicinal product Dossier.

In the process of the expert evaluation of the medicinal product Dossier, the Agency may request the authorisation holder in writing to submit additional information or additional documentation required for the medicinal product quality, safety and efficiency evaluation.

If the applicant fails to submit the requested information in paragraph 2 of this Article within 30 days following the receipt of the written notification by the Agency, the Agency shall refuse the renewal application.

In case specified in paragraph 2 of this Article, the legal 90-day term for approving the renewal application starts from the day of submittance of the requested documentation by the applicant.

UNREVISED VERSION

V TRANSITIONAL AND FINAL PROVISIONS

Article 80

The manufacturer who, pertaining to Law, harmonises the documentation of a medicinal product and manufacturing conditions with the regulations of that Law and the guidelines of Good manufacturing Practice, as well as the manufacturer submitting the first renewal application after the above Law becomes effective, shall submit the medicinal product documentation including Part 1 of the European Dossier pertaining to administrative documentation, expert reports are excluded, and Part 2 European Dossier pertaining to quality of the medicinal product.

In case of applications in paragraph 1 of this Article, the authorisation is granted for the period of five years in which period the authorisation holder shall submit to the Agency the complete medicinal product documentation specified by this Rules, and within the period of five years after the effective date of the Law at the latest.

If the authorisation holder fails to submit the documentation under the conditions specified in paragraph 2 of this Article, the Agency shall make the decision on the cessation of the authorisation.

Article 81

By December 31, 2009 the authorisation may be granted based on the abbreviated documentation referred to in Article 13 paragraph 3, line two of this Rules, upon the submission of the evidence that the reference product essentially similar to the medicinal product covered by the application has been, at the time of application submission for granting authorisation, marketed in the Republic of Serbia, European Union or any other country specifying the same requirements for authorisation granting, not less than six years and not less than 10 years for a medicinal product obtained by biotechnology.

Starting from January 1, 2010, the documentation for authorisation granting as referred to in Article 13 of this Rules can be submitted to the Agency after the expiration of a eight-year period from the first authorisation granted for the reference medicinal product.

In cases specified in paragraph 2 of this Article the Agency is granting authorisation for placing a medicinal product on the market of the Republic of Serbia after the expiration of a 10-year period from the first marketing authorisation of the reference product.

Article 82

This Rules becomes effective eight days after it has been published in "The Official Heralld of the Republic of Serbia".