(Unofficial translation)

RESOLUTION OF THE MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS
No. 100 dated November 18, 2020

On the Requirements for the documents that make up the master file

Amendments and additions:

Resolution of the Ministry of Health of the Republic of Belarus No. 37 dated April 22, 2022 (National register No. 8/38138 dated 25.05.2022);

Resolution of the Ministry of Health of the Republic of Belarus No. 163 dated October 6, 2023 (National register No. 8/40832 dated 19.12.2023);

On grounds of part eight of Article 10 of the Law of the Republic of Belarus No. 161-Z dated July 20, 2006 "On the Circulation of Medicines", the Ministry of Health of the Republic of Belarus RESOLVES:

1. To approve the Instructions on the requirements for the documents that make up the master file (attached).

2. To declare invalid:

Resolution of the Ministry of Health of the Republic of Belarus No. 52 dated May 8, 2009 "On the Requirements for documents submitted for State Registration (confirmation of State Registration) of medicines and pharmaceutical substances";

Resolution of the Ministry of Health of the Republic of Belarus No. 129 dated November 20, 2009 "On Amendments and Additions to the Resolution of the Ministry of Health of the Republic of Belarus No. 52 dated May 8, 2009";

Resolution of the Ministry of Health of the Republic of Belarus No. 124 dated September 13, 2010 "On Amendments and Additions to the Resolution of the Ministry of Health of the Republic of Belarus dated May 8, 2009";

Resolution of the Ministry of Health of the Republic of Belarus No. 52 dated April 17, 2015 "On Amendments and Additions to the Resolution of the Ministry of Health of the Republic of Belarus No. 52 dated May 8, 2009";

Resolution of the Ministry of Health of the Republic of Belarus No. 24 dated February 11, 2016 "On Amending the Resolution of the Ministry of Health of the Republic of Belarus No. 52 dated May 8, 2009";

Resolution of the Ministry of Health of the Republic of Belarus No. 91 dated August 26, 2019 "On Amendments to the Resolution of the Ministry of Health of the Republic of Belarus No. 52 dated May 8, 2009".

3. This Resolution comes into force after its official publication.

Acting Minister **D.L. Pinevich**

AGREED BY
the Ministry of Foreign Affairs
of the Republic of Belarus

APPROVED

Resolution of
the Ministry of Health
of the Republic of Belarus
No. 100 dated November 18, 2020

INSTRUCTIONS
on the Requirements for the documents that make up the master file

1. These Instructions establish the Requirements for the documents that make up the master file.

2. The documents that make up the master file for State Registration (confirmation of State Registration), conditional State Registration (confirmation of conditional State Registration) of a medicinal product shall meet the following requirements:

2.1. the application shall be prepared in the form according to Appendix 1 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.1 "State registration and obtaining a registration certificate for a medicinal product or pharmaceutical substance" or Appendix to the Regulations of the administrative procedure, carried out in relation to the economic entities under sub-clause 9.4.2 "Confirmation of state registration of a medicinal product and obtaining a registration certificate", or Appendix to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.5 "Conditional state registration and obtaining a registration certificate", or Appendix to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.6 "Confirmation of conditional state registration and obtaining a registration certificate for a medicinal product" approved by the Resolution of the Ministry of Health of the Republic of Belarus No. 42 dated May 12, 2022;

2.2. omitted;

2.3. omitted;

2.4. omitted;

2.5. the original or a copy of a document confirming that a legal entity of the Republic of Belarus, an individual entrepreneur registered in the Republic of Belarus, a foreign legal entity, a foreign organization created in accordance with the legislation of foreign states are the official representative of the Holder of the Registration Certificate for a medicinal product, shall be submitted with a translation into Belarusian or Russian certified by the Holder of the Registration Certificate (Applicant, Manufacturer). A copy of the document shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer).

2.6. the original or a copy of the document confirming that the Applicant is a member of the association, which also includes the Manufacturer of the medicinal product, if the Applicant and the Manufacturer of the medicinal product are part of the same association. A copy of the document shall be notarized. A document drawn up in a foreign language shall be accompanied by a translation into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). Documents shall be legalized and apostilled, unless otherwise provided by international treaties of the Republic of Belarus;

2.7. the original or a copy of the document confirming the registration of the medicinal product in the country of the Holder of the Registration Certificate (Manufacturer's country) (Registration Certificate or Certificate of Pharmaceutical Product in the format recommended by the World Health Organization) issued by the authorized body of the country of the Holder of the Registration Certificate (Manufacturer's country). A copy of the document shall be notarized. In the absence of Registration of a medicinal product in the country of the Holder of the Registration Certificate (Manufacturer's country), a notarized copy of the Certificate of Pharmaceutical Product indicating the reasons for the lack of Registration shall be submitted as well as an explanatory note of the Holder of the Registration Certificate justifying the lack of Registration data or a notarized copy of another document issued by the authorized body of the country of the Holder of the

Registration Certificate (Manufacturer's country) explaining the lack of Registration - during State Registration, conditional State Registration of a medicinal product. Documents issued by the authorized body of the country of the Holder of the Registration Certificate (Manufacturer's country) shall be submitted in original or in the form of notarized copy of the original with a translation into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). Documents shall be legalized and apostilled, unless otherwise provided by international treaties of the Republic of Belarus (for medicinal products of foreign manufacture);

2.8. omitted;

2.9. a copy of the license issued by the authorized body of the country of manufacture and granting the right to manufacture the medicinal product. The document shall be submitted when medicinal products are of foreign manufacture and shall be notarized and translated into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). Documents shall be legalized and apostilled, unless otherwise provided by international treaties of the Republic of Belarus;

2.10. a copy of the valid document certifying the manufacture of a medicinal product under Good Manufacturing Practice conditions, issued by the authorized body of the country of manufacture of the medicinal product (for each participant in the manufacture of the medicinal product), shall be notarized. If there is no information in this document about the date of the recent inspection of the specified production, its validity period shall deem to be not more than 3 years from the date of its issue. The document shall be submitted when medicinal products are of foreign manufacture and shall be notarized and translated into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). Documents shall be legalized and apostilled, unless otherwise provided by international treaties of the Republic of Belarus;

In the absence of a copy of a valid document certifying the manufacture of a medicinal product under Good Manufacturing Practice conditions issued by the authorised body of the country of manufacture of the medicinal product (for each participant in the manufacture of the medicinal product), a printout of a graphic screen image (screenshot) of the Internet page of the official website of the regulatory authority in the global computer network Internet containing information on the valid document certifying the manufacture of the medicinal product under Good Manufacturing Practice conditions issued by the authorised body of the country of manufacture of the medicinal product (for each participant in the manufacture of the medicinal product) shall be submitted. A printout of a graphic image of the screen (screenshot) of the website of the official website of the regulatory authority of the country where the medicinal product is manufactured in the global computer network Internet shall be accompanied by a translation into the Belarusian or Russian (the accuracy of the translation or authenticity of the translator's signature shall be notarised). The period of preparation of the printout should not exceed 3 months from the date of submission of documents;

2.11. information on the registration of a medicinal product in other countries shall be submitted during State Registration, conditional State Registration (for medicinal products of foreign manufacture).

Information shall be provided, including a list of countries in which the medicinal product is registered (indicating the name of the medicinal product, the number and date of the Registration Certificate, its validity period), or documents shall be submitted for registration, as well as information on the refusal of registration or suspension of the Registration Certificate (indicating the date of the decision to refuse registration, to suspend the Registration Certificate). The information provided in a foreign language shall be accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer);

2.12. the draft Summary of Product Characteristics of the medicinal product (hereinafter - the SmPC) shall be submitted in two copies in Belarusian or Russian and comply with the Requirements for instructions for the medical use of the medicinal product and the general

characteristics of the medicinal product for medical use, approved by the Eurasian Economic Commission Council Resolution No. 88 dated November 3, 2016.

The draft SmPC shall contain an indication of the procedure for retail sale of the medicinal product: “on prescription” or “without prescription”.

The draft SmPC shall be submitted on paper in A4 format with a sheet margin around the perimeter of at least 1.5 cm and a font size of at least 12 pt.

The information contained in the draft SmPC shall correspond to the information in the SmPC approved by the authorized body of the country of Holder of the Registration Certificate (Manufacturer's country) - for medicinal products of foreign manufacture.

The draft SmPC shall be developed on the basis of the general characteristics of the original (reference) medicinal product registered in the Republic of Belarus. If the original (reference) medicinal product is not registered in the Republic of Belarus, the draft SmPC of the generic medicinal product shall be developed on the basis of the general characteristics of the original (reference) medicinal product approved by the authorized body of the country of the Holder of the Registration Certificate (Manufacturer's country);

2.13. The draft Basic Prescribing Information (package leaflet) shall be submitted in two copies in Belarusian or Russian and comply with the Requirements for instructions for the medical use of the medicinal product and the general characteristics of the medicinal product for medical use, approved by the Eurasian Economic Commission Council Resolution No. 88 dated November 3, 2016.

The draft Basic Prescribing Information (package leaflet) shall contain an indication of the procedure for retail sale of the medicinal product: “on prescription” or “without prescription”.

The draft Basic Prescribing Information (package leaflet) shall be submitted on paper in A4 format with a sheet margin around the perimeter of at least 1.5 cm and a font size of at least 12 pt.

The draft Basic Prescribing Information (package leaflet) shall be developed on the basis of information contained in the SmPC.

The Basic Prescribing Information (package leaflet) of the medicinal product shall be presented in terms understandable to patients (consumers);

2.14. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian shall be presented in color in 3 copies for different packaging and dosages of the medicinal product, indicating the color pantones and the scale of primary, secondary (intermediate - if any) packaging. Information on primary and secondary packaging (intermediate packaging - if any) may be indicated in several languages, provided that the labels contain identical information, which is confirmed by a notarized translation into Belarusian or Russian submitted by the Applicant.

The information in regard of the models of the primary and secondary packaging (intermediate packaging - if any) shall comply with the Requirements for the Labeling of Medicines for Medical Use and Veterinary Medicines, approved by the Eurasian Economic Commission Council Resolution No. 76 dated November 3, 2016, as well as:

the indication of the names of dosage forms, types of primary packaging and components shall be carried out in accordance with the Nomenclature of dosage forms approved by the Resolution of the Collegium of the Eurasian Economic Commission No. 172 dated December 22, 2015;

the indication of the dosage on the packaging models shall be consistent with Appendix 9 of the Requirements for instructions for the medical use of the medicinal product and the general characteristics of the medicinal product for medical use, approved by the Eurasian Economic Commission Council Resolution No. 88 dated November 3, 2016;

indication of dosage, names of dosage forms, types of primary packaging and components shall correspond to other documents that make up the master file.

On the primary or secondary packaging of a medicinal product to be sold without a doctor's prescription, it shall be allowed to apply the full text of the Basic Prescribing Information (package

leaflet). It shall not be allowed to put on the packaging information of an advertising nature or information that does not comply with the Basic Prescribing Information (package leaflet).

Packaging models containing information on marking with a product number in the form of a bar identification code shall be accompanied by its decoding;

2.15. copies of Manufacturer's documents, including a description of the pharmaceutical substance manufacturing process, a concise manufacturing process scheme, information on the size of the industrial batch, methods for confirming the structure, justification of impurities, a declaration of manufacturing process validation or a CEP certificate (if any), reports on validation of quality control methods shall be submitted during State Registration, conditional State Registration of a medicinal product in the absence of registration of a pharmaceutical substance. The documents shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall comply with the following requirements:

2.15.1. the Manufacturer's document, containing a description of the pharmaceutical substance manufacturing process, shall include information on the initial raw materials (structure-forming parts, reagents, catalysts, solvents, etc.) and materials (packaging materials, filters, etc.) used for the manufacture of the pharmaceutical substance with an indication of the stages of manufacture at which they are used, as well as information on control in the manufacturing process and critical stages of this process. For raw materials and materials that are critical in relation to the quality of a pharmaceutical substance, a description of the manufacture methods shall be accompanied by the provision of information on their quality (including data on the absence of the risk of transmitting the pathogens of animal spongiform encephalopathies and viral safety), as well as information confirming compliance with the requirements (standards) for the intended use;

2.15.2. the concise manufacturing process (synthesis) scheme shall be a brief schematic description of the pharmaceutical substance manufacturing process;

2.15.3. information on the size of an industrial batch should be presented in a form suitable for a given pharmaceutical substance (for example, kg, t, l, etc.);

2.15.4. the document containing methods for confirming the structure and justification of impurities shall include data on establishing the structure and other characteristics of a pharmaceutical substance, taking into account the possibility to use modern physicochemical, immunochemical, biological methods (as applicable), as well as information on impurities;

2.15.5. the declaration of validation of the pharmaceutical substance manufacturing process shall confirm that the Manufacturer has carried out a validation with a positive result in respect to the manufacturing process of the declared industrial batches of the pharmaceutical substance. Additionally, information shall be provided on the successful validation of the aseptic and sterilization stages of the pharmaceutical substance manufacturing process;

2.15.6. a copy of the CEP certificate (Certificate of Suitability to the Monographs of the European Pharmacopoeia) shall be submitted in the form of the most up-to-date version. If a CEP certificate is provided, a description of the methods for obtaining a pharmaceutical substance, a document containing methods for confirming the structure and justification of impurities are provided, a declaration of the manufacturing process validation shall not be required;

2.15.7. the reports on the validation of quality control methods for a pharmaceutical substance shall be submitted in the event the State Pharmacopoeia of the Republic of Belarus, the European Pharmacopoeia, the Pharmacopoeia of the Eurasian Economic Union, the United States Pharmacopoeia, the British Pharmacopoeia do not have a certified pharmacopeial monograph for the given pharmaceutical substance or the quality control methods differ from the pharmacopoeia. The reports on the validation of quality control methods shall comply with the criteria of the section II # 5.3.2 "Validation of analytical procedures and trials" of the State Pharmacopoeia of the Republic of Belarus and (or) the Guidelines for the validation of analytical methods for testing medicinal products, approved by the Resolution of the Collegium of the Eurasian Economic Commission No. 113 dated July 17, 2018, and (or) the applicable guidelines of the International

Conference on Harmonization of Technical Requirements for Registration of Medicinal Products (ICH) (hereinafter - the International Conference on Harmonization (ICH));

2.16. a copy of the document on quality control of a pharmaceutical substance shall comply with the requirements for a draft Regulations on the quality of a pharmaceutical substance in accordance with Sub-clause 3.6 of Clause 3 of these Instructions, with the exception of requirements for its preparation. The document shall contain information provided for in section 3.2.S.4 of module 3 of the List of documents in the modules of the medicinal product master file of the Appendix No. 4 to the Rules for the registration and examination of medicinal products for human use, approved by the Eurasian Economic Commission Council Resolution No. 78 dated November 3, 2016 (hereinafter - the Rules for Registration and Examination of medicinal products);

The document shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer);

2.17. copies of the documents on quality control of primary packaging materials of a pharmaceutical substance (components of primary packaging) and copies of documents confirming that primary packaging materials (components of primary packaging) are suitable for use for packaging pharmaceutical substances, shall be submitted during State Registration, conditional State Registration of a medicinal product in the absence of registration of a pharmaceutical substance. The documents shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the following requirements:

2.17.1. contain a description of the packaging and (or) sealing system (components of primary packaging), including a description of the materials from which each component of the primary packaging is made, and also include information confirming that the primary packaging used to store the pharmaceutical substance corresponds to the used in the study of the stability of this pharmaceutical substance;

2.17.2. include specifications for primary packaging materials containing a description, size requirements, drawings, data and characteristics determined by the properties of the pharmaceutical substance (if applicable). When specifying non-pharmacopoeial quality control methods (techniques) in the specification, a description of their implementation shall be provided (if applicable);

2.17.3. as documents confirming that the materials of the primary packaging (components of the primary packaging) are suitable for use for packaging pharmaceutical substances, certificates of conformity, registration certificates, protocols of sanitary and hygienic tests, test reports in accordance with pharmacopoeial requirements, etc. (as relevant). For pharmaceutical substances used for the manufacture of medicinal products intended for oral and external use, it shall be allowed to submit documents confirming the possibility of using these primary packaging materials in the food industry. For pharmaceutical substances intended for the manufacture of medicinal products for external use, it shall be also allowed to submit documents confirming the possibility of using primary packaging materials in the manufacture of cosmetics;

2.18. copies of the Manufacturer's documents containing the results of the study of the stability of the pharmaceutical substance (plan, report, tables with the research results) shall be submitted during State Registration, conditional State Registration of the medicinal product in the absence of registration of the pharmaceutical substance, certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer and shall contain:

2.18.1. information on the scale of the batches on which the stability studies of the pharmaceutical substance were carried out (experimental, industrial or other), the size of these batches, the types of tests performed (long-term, accelerated, intermediate);

information about production sites, conditions under which the research was carried out (temperature, relative humidity, etc.);

information about the pharmaceutical substance packaging system and about the methods used in the study of stability;

conclusion on the establishment of the expiration date and (or) the time frame for the re-examination of the pharmaceutical substance.

The specified information shall correspond to other sections of the master file;

2.18.2. tables with the results of studies of the stability of a pharmaceutical substance shall be presented for all declared types of packaging systems, indicating:

quality indicators, which were monitored in the course of stability studies, as well as established norms;

frequency of control;

results of stability studies.

The results of stability studies shall be presented in an informative form, including tables, allowing the assessment of trends in quality indicators (where possible). Tables with results shall be signed by the performers and the manager, as well as certified by the seal of the organization in which they were held.

The results of studies of stability of photostability and stress tests shall be presented depending on the physicochemical properties of the pharmaceutical substance (if necessary).

In the case of using the matrix method (matrix planning) and the method of bracketing in the study of stability, a justification for their use shall be provided.

The pharmaceutical substance packaging system in the study of stability shall coincide with the packaging system proposed for its storage. The test methods used in the study of the stability of a pharmaceutical substance shall be validated, make it possible to assess its stability and comply with the methods specified in the regulatory document on the quality of a pharmaceutical substance (document on quality control of a pharmaceutical substance).

The plan to study the stability of a pharmaceutical substance, in case the available data do not cover the entire provided shelf life, shall be accompanied by a commitment to continue stability studies after receiving the Registration Certificate.

The Manufacturer's documents containing the results of a study of the stability of a pharmaceutical substance shall confirm that the studies were carried out in accordance with the:

Requirements for the study of stability of medicinal products and pharmaceutical substances, approved by the Resolution of the Collegium of the Eurasian Economic Commission No. 69 dated May 10, 2018;

chapter 8 of the Rules for Research on Biological Medicinal Products of the Eurasian Economic Union, approved by the Eurasian Economic Commission Council Resolution No. 89 dated November 3, 2016, or the guidelines of the International Conference on Harmonization (ICH);

2.19. the Manufacturer's document containing information on the composition of the medicinal product, indicating the amount of all ingredients, including all excipients per dosage unit (for dosed medicinal products) or unit of mass or volume (for non-dosed medicinal products), with reference to quality control documents of pharmaceutical substance and excipients shall contain:

the trade name of the medicinal product;

the name of the manufacturer producing the medicinal product;

type of formulated medicinal product;

dosage of the medicinal product (if the medicinal product contains one or two pharmaceutical substances);

name of ingredients;

the amount of each ingredient;

information on the purpose of the ingredients;

a reference to the quality control document for each ingredient.

The information specified in paragraphs five to eight of the first part of this sub-clause shall be presented in the form of a table.

If a pharmaceutical substance is a salt or a hydrate, its amount shall be expressed in mass units (units of biological activity) of the active part of the molecule of the active substance (base, acid or anhydrous salt), for example, "thorimefene (in the form of thorimefene citrate) - 60 mg". With regard to frequently used pharmaceutical substances in the composition of a medicinal product, the dosage of which is traditionally expressed in salt or hydrated form, the amount may be indicated as a salt or hydrate (for example, "diltiazem hydrochloride - 60 mg"). For a pharmaceutical substance that is an ester or prodrug, its amount shall be indicated as the amount of the ester or prodrug. In the case of powders for the preparation of a solution or suspension for oral use, the amount of a pharmaceutical substance shall be expressed per dosage unit - for a single-dose medicinal product, or per volume dose unit after reconstitution - for a multi-dose medicinal product. For dosed inhalation drugs, the amount of a pharmaceutical substance shall be indicated on the delivered dose and (or) metered dose. For parenteral medicinal products, with the exception of reconstituted powders, in the case of "full use of the contents of the primary package" - the amount of the pharmaceutical substance shall be indicated by the mass (volume) of the primary package (ampoule, vial, etc.) or the total declared volume, in the case of "partial use of the contents of the primary packaging" - the amount of the pharmaceutical substance per milliliter and the total declared volume shall be indicated.

Information on the included excess of the amount of ingredients included in the composition of the medicinal product shall be indicated, if applicable.

The ingredients that are removed during the manufacturing process (for example, granulating liquids, solvents, etc.) shall not be specified in the composition of the medicinal product, but the information on the ingredients that are used as the circumstances require (for example, acids or alkalis to adjust the pH value) shall be specified.

Flavorings used in medicinal products shall meet the requirements of the Customs Union Technical Regulations “Safety Requirements for Food Additives, Flavorings, and Technological Aides” (TR CU 029/2012), adopted by the Resolution of the Council of the Eurasian Economic Commission No. 58 dated July 20, 2012. In this case, information on the composition of flavorings shall be as complete as possible, it shall be allowed not to indicate confidential information about the flavoring composition.

In the case of printing on tablets, capsules and other medicinal products, information on the composition of the ink used shall be provided.

For medicinal products in the form of coated tablets, the composition of the core and the composition of the shell shall be separately indicated, and for medicinal products in the form of capsules - the composition of the capsule shell and its contents.

Excipients shall be indicated in such a way that they are not mistaken for excipients with a similar chemical structure (for example, starch, sodium starch glycolate, pregelatinised starch).

For pharmaceutical substances and excipients, references shall be made to quality control documents (for example, pharmacopoeial monographs or Manufacturers' specifications), for excipients, their functional purpose shall additionally be indicated. For film-coated tablets, capsules and the like, reference shall be made to the quality control document for both the ready-mixed film-coat of capsule shell and the ingredients of which they are composed;

The document shall be drawn up in Belarusian or Russian and certified by the Holder of the Registration Certificate (Applicant, Manufacturer);

2.20. a copy of the document on pharmaceutical development shall be submitted during State Registration, conditional State Registration of a medicinal product, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall contain information about development studies carried out in order to prove that the dosage form, composition, manufacturing process, selected packaging (sealing) system, microbiological characteristics, instructions for preparing the medicinal product for use correspond to the intended use specified by the Applicant in the master file.

The document on the pharmaceutical development of a medicinal product shall include such sections as the components of the medicinal product (pharmaceutical substance, excipients), medicinal product (development of the dosage form, production surpluses, physicochemical and biological properties), development of the manufacturing process, packaging (sealing) system, microbiological characteristics, compatability.

In the course of pharmaceutical development, the studied compositions of the medicinal product and the critical parameters of the manufacturing process that may affect batch reproducibility, pharmacological effect and quality of the medicinal product shall be identified and described.

The information contained in the document on the pharmaceutical development of a medicinal product shall confirm that the development was carried out in accordance with the guidelines of the International Conference on Harmonization (ICH) or international legal acts constituting the law of the Eurasian Economic Union in the field of medicine circulation, including:

Guidelines on the quality of medicinal products for inhalation and nasal medicinal products (annex to the Recommendation of the Collegium of the Eurasian Economic Commission No. 17 dated September 7, 2018) - for medicinal products for inhalation and nasal medicinal products;

The Rules for Research on Biological Medicinal Products of the Eurasian Economic Union, approved by the Eurasian Economic Commission Council Resolution No. 89 dated November 3, 2016, - for biological medicinal products;

Guidelines for the quality of medicinal products with delayed release for oral use (Appendix to the Recommendation of the Collegium of the Eurasian Economic Commission No. 2 dated January 16, 2018) - for medicinal products with delayed release;

2.21. Copies of reports on physicochemical and biological studies to confirm comparability with the original (reference) medicinal product shall be submitted during State Registration of a biosimilar medicinal product, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall include data on the establishment and comparison of physicochemical and biological characteristics, as well as the interpretation of any differences between biosimilar and original (reference) medicinal products.

The documents shall be accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer);

The applicability of a biosimilar approach to a specific biological medicinal product shall be justified.

Reports on physicochemical and biological studies to confirm the comparability of a biosimilar medicinal product with an original (reference) medicinal product shall confirm:

that the research was carried out in accordance with the Rules for Research on Biological Medicinal Products of the Eurasian Economic Union, approved by the Eurasian Economic Commission Council Resolution No. 89 dated November 3, 2016;

the ability of the methods used to detect minor differences between the parameters affecting the assessment of the quality of a biosimilar medicinal product. At the same time, in order to qualify and standardize comparability research methods, it shall be necessary to use official reference materials and materials (pharmacopeial reference materials and materials of the World Health Organization).

Comparison of physicochemical properties shall include not only an assessment of the corresponding parameters, but also the establishment of the structure of related compounds and related impurities. The definition of composition, physical properties, primary structure and higher order structures, amino acid sequence shall be provided. Where appropriate, the N- and C-terminal amino acid sequences, free SH-groups and disulfide bridges shall be compared. All modifications and/or shortenings shall be assessed, and the intrinsic (immanent) or expression system associated variability described. It shall be necessary to compare post-translational modifications, carbohydrate structures.

In order to determine biological activity, appropriate biological quantification methods based on various complementary principles shall be used. Quantitative biological methods shall be

confirmed to be sensitive, specific, and of sufficient discriminatory power. If possible, the results of the relevant biological method shall be presented in calibrated (graded) against international or national reference materials (if available) units of activity;

2.22. copies of the Manufacturer's documents, including a description of the medicinal product manufacturing process, quality control of intermediates, a concise manufacturing process scheme, batch formula, batch size, manufacturing process validation report or manufacturing process validation master plan and a guarantee obligation to provide a manufacturing process validation report, and a report on the fulfillment of obligations to validate the manufacturing process (submitted following the implementation of the obligations, but at least once a year), shall be submitted during State Registration, conditional State Registration of a medicinal product of domestic manufacture.

Copies of the Manufacturer's documents, including a description of the medicinal product manufacturing process, quality control of intermediates, a concise manufacturing process scheme, batch formula, batch size, manufacturing process validation report, shall be submitted during State Registration, conditional State Registration of a medicinal product of foreign manufacture and in case of placing an order by a national Holder of a Registration Certificate (Manufacturer) for performing one or several stages of the technological process of manufacturing a medicinal product outside the Republic of Belarus.

The documents listed in parts one and two of this Sub-clause shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall comply with the following requirements:

the description of the medicinal product manufacturing process (manufacture methods) shall be presented in such a way as to form an idea of the nature of the operations performed, be comprehensive, consistent and make it possible to draw a conclusion about which parameters are critical for the manufacturing process and which are of an auxiliary nature. If necessary, the description of the medicinal product manufacturing process (manufacturing methods) shall include a description of individual process details, information on the type (size) of equipment used. The description of the manufacturing process shall be in an appropriate manner supported by the development data (in particular with respect to all conditions and ranges of values for the parameters of this manufacturing process). Information about production sites involved in the manufacture of a medicinal product (name and address of a manufacturer) shall correspond to those specified in the master file;

quality control of intermediate products shall be consistent with the established critical stages of the manufacturing process, include all types of in-process control and be accompanied by the presentation of specifications for intermediate products and information on quality control procedures;

a concise manufacturing process scheme shall be a brief schematic description of the methods for medicinal product manufacturing with an indication of each stage of the manufacturing process, the corresponding in-process control and a designation of each stage, at which materials are introduced into manufacture;

the batch formula shall reflect information about the composition of a standard industrial batch. If there are batches of different sizes, the composition of each shall be indicated. The batch formula shall contain an indication of the names and quantities of all ingredients used in the manufacturing process, including information on the included excess. Ingredients that are removed from the product during the manufacturing process (for example, granulating liquids, solvents, gases) shall also be specified, but their content may be specified as a range of values, and ingredients that are used as the circumstances require (for example, acids or alkali to adjust the pH value) shall also be specified. If the used amount of a pharmaceutical substance is calculated from the actual quantitative content of this pharmaceutical substance (factorization), then such data shall be indicated and justified;

the size of the industrial batch shall contain information on the number of dosage units (tablets, capsules, ampoules, etc.) or the number of primary packaging (tubes, vials, etc.);

the report on the validation of the medicinal product manufacturing process shall include a description, the results of the validation and comply with the Guidelines for the Validation of the Manufacturing Process of Medicinal Products for Medical Use (annex to the Recommendation of the Collegium of the Eurasian Economic Commission No. 19 dated September 26, 2017) or the guidelines of the International Conference on Harmonization (ICH). For biotechnological (biological) medicinal products, the validation of the medicinal product manufacturing process shall be accompanied by the submission of information on the validation of the pharmaceutical substance manufacturing process;

the validation master plan in regard to the medicinal product manufacturing process shall determine the scope and procedure for conducting validation studies and comply with the requirements for the process validation plan set forth in Appendix No. 1 to the Guidelines for Validating the Manufacturing Process of Medicinal Products for Medical Use (Appendix to the Recommendation of the Collegium of the Eurasian Economic Commission No. 19 dated September 26, 2017). If, together with the validation plan, a report on the validation of the manufacturing process is not submitted, it shall be necessary to submit a guarantee obligation to conduct validation studies and provide a report on the validation of the manufacturing process for the first three industrial batches of the medicinal product before its release for sale. At the same time, guarantee obligations may not be presented for non-standard products or processes set forth in Appendix No. 2 to the Guidelines for Validating the Manufacturing Process of Medicinal Products for Medical Use (Appendix to the Recommendation of the Collegium of the Eurasian Economic Commission No. 19 dated September 26, 2017). In such cases, the master file shall provide data on the validation of industrial-scale batches.

The Manufacturer's documents, including a description of the medicinal product manufacturing process, quality control of intermediate products, a concise manufacturing process scheme, batch formula, and the size of an industrial batch, shall comply with international legal acts that constitute the law of the Eurasian Economic Union in the field of medicine circulation, including:

Guidelines for the production of finished dosage forms of medicinal products (Annex to the Recommendation of the Collegium of the Eurasian Economic Commission No. 3 dated January 29, 2019);

The Rules for Research on Biological Medicinal Products of the Eurasian Economic Union, approved by the Eurasian Economic Commission Council Resolution No. 89 dated November 3, 2016;

Guidelines on the quality of medicinal products for inhalation and nasal medicinal products (Annex to the Recommendation of the Collegium of the Eurasian Economic Commission No. 17 dated September 7, 2018);

Guidelines on the quality of herbal medicines (Annex to the Recommendation of the Collegium of the Eurasian Economic Commission No. 6 dated May 10, 2018).

In cases where an order is placed by a national Holder of the Registration Certificate (Manufacturer) to perform one or several stages of the technological process of medicinal product manufacture outside the Republic of Belarus, the documents specified in paragraphs two to eight of part three of this Sub-clause shall be submitted, taking into account the distribution of functions between manufacturers participating in the medicinal product manufacturing process;

2.23. copies of documents on quality control of excipients shall be submitted during State Registration, conditional State Registration of a medicinal product, certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall include:

a specification containing references to test methods and a description of quality control procedures. If the quality control of the excipient is carried out in accordance with the

pharmacopoeial monograph of the State Pharmacopoeia of the Republic of Belarus, the European Pharmacopoeia, the Pharmacopoeia of the Eurasian Economic Union (hereinafter - the Pharmacopoeia), instead of submitting a document on quality control, a reference to the pharmacopoeial monograph of the corresponding pharmacopoeia may be indicated. In the event that an excipient included in the pharmacopoeia is obtained by a method in which impurities that are not controlled by the pharmacopoeial monograph of the pharmacopoeia may occur, then the specification shall indicate these impurities and the norms (permissible limits) established for them, and also present the method of their determination. In the event that the requirements of the pharmacopoeial monograph of the pharmacopoeia are insufficient to ensure the quality of the excipient, a more detailed specification shall be required, taking into account the peculiarities of manufacture, the quality requirements established by the manufacturer, and the intended use.

Excipients quality control documents shall:

comply with the requirements of the General Pharmacopoeia Monograph of the State Pharmacopoeia of the Republic of Belarus 01/2013: 2034 "Substances for pharmaceutical use";

contain a description of the manufacturing process, information on chemical, pharmaceutical, biological properties, a description of methods and techniques used in quality control, confirmed safety data - for excipients that are used for the first time in a medicinal product or are used with a new route of administration for these excipients;

be accompanied (if applicable) by copies or digitized photographs, chromatograms, spectra, photomicrographies, drawings, etc.;

2.24. the draft normative document on quality shall be prepared in Belarusian and Russian and contain information in accordance with sections 3.2.P.5.1 and 3.2.P.5.2 of module 3 of the List of documents in the modules of the master file of the medicinal product of Appendix No. 4 to the Rules for Registration and Examination of medicinal products.

The draft normative document on quality shall contain the following sections: title page; specification; description of test methods, packaging; marking.

The title page of the draft normative document on quality shall be drawn up in the form in accordance with Appendix 2.

The specification shall comply with the original Manufacturer's specification (for example, comply with section 3.2.P.5.1 of module 3 of the List of documents in the modules of the master file of a medicinal product in Appendix No. 4 to the Rules for the registration and examination of medicinal products). The specification shall be presented in the form of a table consisting of 3 columns: quality indicators, norms (permissible limits), links to test methods.

The names of quality indicators shall be indicated in accordance with the pharmacopoeial monographs of the State Pharmacopoeia of the Republic of Belarus.

Quality indicators and norms (permissible limits) shall be established in accordance with the requirements of the general pharmacopoeial monographs of the State Pharmacopoeia of the Republic of Belarus, and in their absence - in accordance with the requirements of the general pharmacopoeial monographs of the European Pharmacopoeia and (or) the Pharmacopoeia of the Eurasian Economic Union, taking into account the specifics of a specific dosage form of a medicinal product, depending on the physicochemical (biological) properties of the pharmaceutical substance.

The normative document on quality shall include a description of universal tests applicable to all medicinal products, as well as a description of specific tests typical for certain dosage forms.

Universal tests include: description, authenticity (identification); quantitation; accompanying impurities. Cases of non-inclusion of any test in the normative document on quality shall be justified.

The inclusion in the normative document on quality of certain specific tests shall be determined by the characteristics of this particular dosage form.

The Manufacturer's specification may provide for the establishment of stricter acceptance criteria for the release of a medicinal product in comparison with the acceptance criteria applied during the shelf life (storage).

For individual tests (for example, "microbiological purity"), the specification may include a test frequency.

The specification may exclude in-house tests that are used to correct process parameters within the operating range specified for the process (for example, hardness and fragility of the tablet cores to be coated and the weight of individual tablets).

When justifying the exclusion of a test from the specification, it shall be necessary to be guided by the data on the development and validation of the medicinal product manufacturing process (if applicable).

The description of the medicinal product test methods for all quality indicators specified in the specification, with references to the State Pharmacopoeia of the Republic of Belarus, shall be given in accordance with the original description of the medicinal product test methods by the Manufacturer (for example, the description of the test methods shall comply with section 3.2.P.5.2 of module 3 of the List of documents in the modules of the master file of the medicinal product in Appendix No. 4 to the Rules for the registration and examination of medicinal products).

When describing the quality control methods, after the section heading, shall be indicated in the following order: a link to the section, pharmacopoeial monograph or page of the State Pharmacopoeia of the Republic of Belarus in accordance with the method used; norm (permissible limits), equipment (if necessary), a list of reference materials and their qualifications, a method for preparing reagents and (or) solutions, if they are not described in the State Pharmacopoeia of the Republic of Belarus, and a test method.

When testing by methods that provide for obtaining spectra, chromatograms, electrophoregrams, etc., their samples shall be included in the draft normative document on quality.

If the State Pharmacopoeia of the Republic of Belarus contains descriptions of the characteristics of reagents, standard solutions, buffer solutions and materials used in testing, their names shall be italicized and marked by the symbol "P" after the name. If the State Pharmacopoeia of the Republic of Belarus does not contain descriptions of the characteristics of reagents, standard solutions, buffer solutions and materials used in testing, it shall be necessary to indicate their designations, qualifications and (or) the Manufacturer's documents regulating their quality, indicating the name. The names of titrated solutions described in the State Pharmacopoeia of the Republic of Belarus shall also be italicized, without the symbol “P”. When reference materials are used in testing, their qualification and Manufacturer's name or a reference to the corresponding pharmacopoeia shall be indicated.

Calculation formulas shall be presented in expanded and abbreviated forms and accompanied by an explanation of the physical values indicated in them. The designations of physical values shall be given in accordance with the requirements of the State Pharmacopoeia of the Republic of Belarus. Carrying-over part of the calculation formula to another line shall not be allowed.

To measure the physical values specified in the normative document on quantity, the units of measurement provided by the International System of Units (SI system) and the units of measurement used on an equal basis with them shall be used.

Requirements for individual sections of the normative document on quantity:

in the "Description" section, the color shall be characterized by names: white, blue, green, yellow, orange, red, etc. The acceptable range of colority shall be within the tone range. In case of color tones, the color contained in the least shall be indicated in the first place, the predominant color shall be indicated with a hyphen. For example, "tablets are green with a brownish tone or brownish-green". For lightly colored samples, the name of the color shall be characterized by the suffix "-ish" or indicated "light-". For example, "yellowish" or "light yellow". The smell shall be characterized by the terms: "odorless", "with a characteristic odor", "with a faint odor";

the section "Residual quantities of organic solvents" shall be included in the normative document on quality in accordance with the approaches given in the general pharmacopoeial monograph of the State Pharmacopoeia of the Republic of Belarus "5.4. Residual quantities of organic solvents";

the section "Microbiological purity" shall indicate the presence or absence of antimicrobial action, a description of the sample preparation, indicating the amount of sample and diluent (for each dilution); if a membrane filtration method is used, indicate the amount of flushing liquid; give a brief description of the method and conditions of inoculation of medium;

in the sections "Abnormal toxicity", "Pyrogenicity", "Content of substances of histamine-like action", the test doses, route of administration, observation period shall be indicated;

the section "Bacterial endotoxins" shall indicate the presence (absence) of interfering factors, concentration in the initial solution (preparation conditions, if necessary);

the section "Sterility" shall provide a summary of the methods (direct inoculation or membrane filtration).

If the method and (or) the test procedure specified in the normative document on quality are described in the general pharmacopoeia monograph of the State Pharmacopoeia of the Republic of Belarus, a reference to the source shall be indicated without a description of the method and (or) test procedure, indicating, if necessary, sample preparation. When the methods described in the pharmacopoeias of other states are included, a complete description of the methods and (or) test methods used shall be included in the normative document on quality.

Terms, designations and definitions shall comply with the State Pharmacopoeia of the Republic of Belarus. When using terms and designations that are not defined by the State Pharmacopoeia of the Republic of Belarus and are not generally recognized, their definitions shall be given in the text.

The text of the normative document on quality shall be short, without repetitions and exclude the possibility of double interpretation. Abbreviations of words in the text, names of figures and diagrams shall not be allowed, with the exception of abbreviations contained in the specification and established by the State Pharmacopoeia of the Republic of Belarus.

Requirements for the quality of the medicinal product shall be stated in the imperative form, and the test methods - in the third person plural.

In the text it shall be not allowed to use:

colloquial speech;

various terms that are close in meaning (synonyms) for the same concept, as well as foreign words and terms in the presence of equivalent words and terms in the Russian language;

abbreviations of units of measurement, if they are used without numbers;

replacing of words with letter symbols (except for tables and formulas);

mathematical signs without numbers.

The text of the normative document on the quality of the medicinal product shall be drawn up as follows:

one-sided printing;

margin sizes: left - 30 mm, right - 15 mm, top and bottom - 20 mm;

paragraph indentation - 12.5 mm;

Times New Roman font, size 14 (for the number of the normative document on quality - 16);

the titles and name of the medicinal product shall begin with a capital letter and be in bold;

the main text shall be printed at 1.5 line spacing, text in specifications and notes - at 1 line spacing, text in headings - at 1 line spacing;

the pages of the normative document on the quality shall be numbered. In this case, the number shall not be put on the first page;

figures, flow charts, diagrams, graphs, spectra and chromatograms may be presented on separate pages or given in the text of the normative document on quality.

The inclusion of the sections "Storage", "Shelf life" in the draft normative document on quality shall not be required.

The section "Packaging" of the draft normative document on quality shall contain the phrase "In accordance with clause 8 of the Application for State Registration (confirmation of State Registration), conditional State Registration (confirmation of conditional State Registration) of a

medicinal product, taking into account the amendments introduced under this section (if any)". Providing any additional information shall not be required in this section.

The section "Marking" of the draft normative document on quality shall contain the phrase "In accordance with the presented packaging models". Providing any additional information shall not be required in this section.

With regard to the document on quality control of bulk or intermediate products of foreign manufacture, submitted in the case of placing an order for the industrial production of a medicinal product from a foreign Manufacturer, the requirements for the draft normative document on quality shall be applicable, with the exception of the requirements for its preparation. In addition, if applicable, the document on quality control of a foreign Manufacturer shall comply with section 3.2.P.5 of module 3 of the List of documents in the modules of the master file of a medicinal product of Appendix No. 4 to the Rules for Registration and Examination of medicinal products;

2.25. copies of reports on the validation of quality control methods for a medicinal product, shall be submitted during State Registration, conditional State Registration of a medicinal product, certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by the translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall be developed in accordance with the requirements of section # 5.3.2 "Validation of analytical methods and tests" of the State Pharmacopoeia of the Republic of Belarus and (or) in accordance with the Guidelines for the Validation of Analytical Methods for Testing Medicines, approved by the Resolution of the Collegium of the Eurasian Economic Commission No. 113 dated July 17, 2018 and (or) the top management of the International Conference on Harmonization (ICH). Validation reports shall include a description of the validated methods or unambiguous references to them, and also include (or be attached to the reports) samples of graphic information (spectra, figures, chromatograms, photographs, etc.). In the case of a wider range of experiments and tests than provided for by the methodology included in the normative document on quality, a full description of the relevant experiments, tests and the results obtained for them shall be provided. It shall not be allowed to present a validation report as a summary of the tests performed. The parameter values of suitability (number of theoretical plates, resolution, etc.) obtained during the validation of methods shall be comparable with the criteria for suitability given in the draft normative document on quality.

Copies of reports on validation of medicinal product quality control methods shall be supplemented with information on the transfer of test methods, including a comparative analysis of the results obtained in the transmitting and receiving laboratories, in cases where an order is placed by the national Holder of the Registration Certificate (Manufacturer) for one or more stages of technological process of medicinal product manufacturing outside the Republic of Belarus;

2.26. copies of documents confirming the quality of one batch of a medicinal product, pharmaceutical substance, excipients, certified by the Holder of the Registration Certificate (Applicant, Manufacturer), shall be accompanied by a translation into Belarusian or Russian.

A document confirming the quality of one batch of a medicinal product shall include the name of the Manufacturer of the medicinal product, the country of manufacture, the trademark (if any), the name of the medicinal product, the type of dosage form, the size and type of packaging, dosage or activity (for one- and two-component medicinal products), batch number, manufacture date and expiration date, quality indicators and standards established for them, references to analytical methods, test results, date of signing and signature of the authorized person who issued the batch release, position, confirmation that the batch of the medicinal product manufactured in accordance with the requirements of Good Manufacturing Practice and the master file.

The quality indicators and the standards established for them included in the document confirming the quality of one batch of the medicinal product shall comply with those specified in the specification for the release of the draft normative document on quality.

For immunological medicinal products (vaccines, toxoids, toxins, sera, immunoglobulins), the Manufacturer shall submit a document confirming the quality of one batch, including a

summary protocol for a batch of an immunological medicinal products in accordance with the recommendations of the World Health Organization.

A document confirming the quality of one batch of a pharmaceutical substance shall include the name of the Manufacturer of the pharmaceutical substance, the country of manufacture, the trademark (if any), the name of the pharmaceutical substance, information about the production site, batch number, manufacture date and expiration date (date of retesting), quality indicators and standards established for them, references to analytical methods, test results, date of signing and signature of the authorized person who issued the batch release, position.

The documents confirming the quality of one batch of a pharmaceutical substance shall be drawn up by the Manufacturer of the pharmaceutical substance and the Manufacturer of the medicinal product (the results of the incoming control). If a certificate of quality for a pharmaceutical substance issued by a Supplier is presented, information on the Manufacturer of the pharmaceutical substance shall be indicated.

The document confirming the quality of one batch of an excipient shall include the name of the Manufacturer of the excipient, the country of manufacture, the trademark (if any), the name of the excipient, information about the production site, the batch number, the date of manufacture and the date of expiration or retesting, quality indicators and the standards established for them, references to analytical methods, test results. Providing of additional information shall be allowed.

A document confirming the quality of one batch of an excipient shall be drawn up by the Manufacturer of the excipient and the Manufacturer of the medicinal product (the results of the incoming inspection).

In the case of presentation of a quality certificate for an excipient issued by a Supplier, information on the Manufacturer of the excipient shall be indicated;

2.27. copies of documents confirming the quality of reference materials used in quality control of a medicinal product shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by the translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall contain the name of the reference standard, the name of the Manufacturer of the reference standard, batch number, general description, scope, certified value properties, each of which is accompanied by an indication of uncertainty, the method used to obtain property values, shelf life, storage conditions.

The document confirming the quality of the secondary reference materials shall reflect their traceability to the primary reference standards.

When using pharmacopoeial reference materials for a purpose other than the intended use, a document shall be submitted to prove their suitability for the other purpose.

2.28. copies of documents on quality control of primary packaging materials (primary packaging components) and copies of documents confirming that the primary packaging materials (primary packaging components) of a medicinal product are suitable for use for packaging a medicinal product, shall be submitted during State Registration, conditional State Registration of a medicinal product, certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by the translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall include:

2.28.1. a description of the packaging or sealing system (components of the primary packaging), including a description of the materials from which each component of the primary packaging is made;

2.28.2. specifications for primary packaging materials. Packaging specifications shall include, if applicable, a description, dimensional requirements, drawings, data and characteristics as determined by the dosage form. When specifying non-pharmacopoeial methods (techniques) in the specification, information on their use shall be provided;

2.28.3. copies of documents confirming that the materials of the primary packaging (components of the primary packaging) of the medicinal product are suitable for use for packaging medicinal products (certificates of conformity, registration certificates, protocols of sanitary and hygienic tests, test reports in accordance with pharmacopoeial requirements, etc., depending on

what is applicable). For medicinal products for oral administration and external use, it shall be allowed to submit documents confirming the possibility of using primary packaging materials in the food industry. For medicinal products for external use, it shall be allowed to provide documents confirming the possibility of using primary packaging materials in the manufacture of cosmetics;

2.29. copies of documents confirming the quality of one batch of materials for the primary packaging of the medicinal product (components of the primary packaging) shall be submitted during State Registration, conditional State Registration of the medicinal product, drawn up by the Manufacturer of the primary packaging material (components of the primary packaging) and the Manufacturer of the medicinal product (the results of incoming control), shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and accompanied by the translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer);

2.30. copies of the Manufacturer's documents containing the results of the study of the stability of the medicinal product (plan, report, tables with the results of the studies) shall be submitted during State Registration, conditional State Registration of the medicinal product, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by the translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall contain:

2.30.1. information on the scale of the batches on which the research was carried out (pilot scale, industrial or other), the size of these batches, the types of tests performed (long-term, accelerated, intermediate), information on production sites, the conditions under which the research was carried out (temperature, relative humidity etc.), the composition of the medicinal product, the Manufacturer (s) of the pharmaceutical substance (s), the justification of the specification for the stability study, information on the packaging system of the medicinal product (primary, secondary, intermediate - if any), on the methods used in the study of stability, the conclusion on the establishment of the shelf life of the medicinal product. The submitted data shall correspond to other sections of the master file;

2.30.2. the tables with the results of stability studies of the medicinal product shall contain information on the quality indicators that were monitored during the stability study and the established rates, instructions on the frequency of control, the results of stability studies. Information on the results of studies shall allow an assessment of trends in the stability of the medicinal product. Tables with results shall be signed by the performers and the manager, as well as certified by the seal of the organization in which they were held.

Stability study data shall be submitted for all declared dosages, packaging of the medicinal product and in all declared packaging systems. The results of photostability studies and stress tests shall be presented depending on the physicochemical properties of the ingredients constituting the medicinal product (if applicable). In the case of using the matrix method (matrix planning) and the method of bracketing, the possibility of their use shall be justified and confirmed.

The description of the packaging system of the medicinal product in the submitted documents on the stability study shall coincide with that proposed for storage, and the test methods for the medicinal product used in the stability studies shall be validated, allowing to assess the stability of the medicinal product and comply with the methods specified in the draft normative document on quality.

For medicinal products in multi-dose containers, if necessary, the stability after the first opening of the package shall be additionally assessed, as well as data confirming the effectiveness of the selected antimicrobial preservatives shall be presented. For medicinal products that require preparation before use (dissolution, dilution, etc.), the stability of the ready-to-use medicinal product (for example, prepared suspension, solution after dilution and during administration, compatibility with medical devices intended for administration, etc.) shall be assessed.

Documents on the study of the stability of the medicinal product shall confirm that they were carried out in accordance with the Requirements for the study of the stability of medicinal products and pharmaceutical substances, approved by the Resolution of the Collegium of the Eurasian

Economic Commission No. 69 dated May 10, 2018, chapter 8 of the Rules for research of biological medicinal products of the Eurasian Economic Union approved by the Resolution of the Council of the Eurasian Economic Commission No. 89 dated November 3, 2016, or the guidelines of the International Conference on Harmonization (ICH);

2.31. copies of reports on preclinical (nonclinical) studies of a medicinal product (with the exception of generic medicinal products) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and submitted during State Registration, conditional State Registration of the medicinal product in electronic format in Belarusian, Russian or English.

The report on preclinical (nonclinical) studies of the medicinal product shall include sections according to the List in accordance with Appendix 3.

A brief description of the performed preclinical (nonclinical) studies of the medicinal product, attached to the report on preclinical (nonclinical) studies of the medicinal product, drawn up in a foreign language, shall be submitted on paper, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and accompanied by a translation into Belarusian or Russian language, certified by the Holder of the Registration Certificate (Applicant, Manufacturer).

If it is not possible to fill in any section (subsection) in the report on preclinical (nonclinical) studies of a medicinal product, a justification shall be provided with references to regulatory legal acts or publications in peer-reviewed scientific medical publications.

Reports on preclinical (nonclinical) studies of medicinal products shall contain information confirming the compliance of the preclinical (nonclinical) studies with the requirements of the Rules of Good Laboratory Practice of the Eurasian Economic Union in the field of medicine circulation, approved by the Resolution of the Council of the Eurasian Economic Commission No. 81 dated November 3, 2016.

Reports on preclinical (nonclinical) studies of original medicinal products shall be submitted in accordance with the requirements for the documents of the master file given in module 4, Appendix No. 1 to the Rules for Registration and Examination of medicinal products.

Reports on preclinical (nonclinical) studies on the safety of medicinal products shall confirm that preclinical (nonclinical) studies were carried out in accordance with the Guidelines for preclinical safety studies for the purpose of conducting clinical trials and registration of medicinal products, approved by the Resolution of the Collegium of the Eurasian Economic Commission No. 202 dated November 26, 2019.

Reports on preclinical (nonclinical) studies on the safety of biotechnological medicinal products shall confirm that preclinical (nonclinical) studies were carried out in accordance with the requirements of chapters 5.3 and 5.4 of the Rules for conducting research on biological medicinal products of the Eurasian Economic Union, approved by the Resolution of the Council of the Eurasian Economic Commission No. 89 dated November 3, 2016;

2.32. copies of reports on clinical studies (trials) of a medicinal product (hereinafter, unless otherwise specified, Clinical Trials) of I – III phases (stages) for original medicinal products conducted in accordance with Good Clinical Practice - during State Registration; Phases (stages) I, II for original medicinal products - during conditional State Registration, certified by the Holder of the Registration Certificate (Applicant, Manufacturer), shall be submitted in electronic form in Belarusian, Russian or English.

The section of the report on the conducted Clinical Trials containing a brief description of the Clinical Trial (hereinafter referred to as the Synopsis), drawn up in a foreign language, shall be submitted on paper, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer).

Copies of reports on Clinical Trials shall be submitted in accordance with the requirements for the documents of the master file given in Module 5, Appendix No. 1 to the Rules for Registration and Examination of medicinal products, while the types and goals of Clinical Trials shall be determined in accordance with the Guidelines on General Issues of Clinical Trials

(Appendix to the Recommendation of the Collegium of the Eurasian Economic Commission No. 11 dated July 17, 2018).

The structure and content of the report on Clinical Trials shall comply with the requirements set out in Appendix No. 1 to the Rules of Good Clinical Practice of the Eurasian Economic Union, approved by the Resolution of the Council of the Eurasian Economic Commission No. 79 dated November 3, 2016.

Copies of reports on Clinical Trials for a biological medicinal product shall be submitted in accordance with Clause 12 of the special requirements for the documents of the master file of certain types of medicinal products of Appendix No. 1 to the Rules for Registration and Examination of medicinal products and contain information confirming compliance with the requirements of the Rules for conducting research on biological medicinal products of The Eurasian Economic Union, approved by the Resolution of the Council of the Eurasian Economic Commission No. 89 dated November 3, 2016.

Copies of reports on Clinical Trials for a radiopharmaceutical medicinal product shall be submitted in accordance with Clause 13 of the special requirements for the documents of the master file of certain types of medicinal products in Appendix No. 1 to the Rules for Registration and Examination of medicinal products.

Copies of Clinical Trial reports for the original combination medicinal product shall contain information confirming that these studies were carried out in accordance with the Guidelines for preclinical and clinical development of combination medicinal products (Appendix to the Recommendation of the Collegium of the Eurasian Economic Commission No. 25 dated September 2, 2019).

Copies of reports on Clinical Trials for herbal medicinal products shall be submitted in accordance with Clause 15 of the special requirements for the documents of the master file of certain types of medicinal products of Appendix No. 1 to the Rules for Registration and Examination of medicinal products.

Copies of reports on Clinical Trials for a homeopathic medicinal product with declared indications for medical use shall be submitted in accordance with Clause 14 of special requirements for documents of the master file of certain types of medicinal products of Appendix No. 1 to the Rules for Registration and Examination of medicinal products;

2.33. copies of reports on study (trial) of bioequivalence (bioavailability) in accordance with Good Clinical Practice and reports on biopharmaceutical studies for generic medicinal products, hybrid medicinal products shall be submitted during State Registration of the medicinal product (not submitted for medicinal product from medicinal plant materials). The above copies of the reports shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and submitted in electronic form in Belarusian, Russian or English.

Sections of the report on Clinical Trials containing a brief description of the study (trial) of bioequivalence (bioavailability) (Synopsis) and a brief description of the biopharmaceutical study, drawn up in a foreign language, shall be submitted on paper, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer).

Copies of reports on conducted studies (trials) of bioequivalence (bioavailability) and biopharmaceutical studies (in vitro studies (including comparative dissolution kinetics test), studies establishing the correlation of results obtained in vitro and in vivo) shall confirm that these studies were carried out in accordance with the Rules for conducting bioequivalence studies of medicinal products within the framework of the Eurasian Economic Union, approved by the Resolution of the Council of the Eurasian Economic Commission No. 85 dated November 3, 2016 (hereinafter - the Rules for Conducting Bioequivalence Studies).

A copy of the report on the study (trial) of bioequivalence (bioavailability) shall comply with Appendix No. 7 to the Rules for Conducting Bioequivalence Studies.

A copy of the report on studies (trials) of bioequivalence for generic or hybrid medicinal products with modified release shall contain information confirming compliance with the Rules for Conducting Bioequivalence Studies.

A copy of the report on bioequivalence studies (trials) for the reproduced combination medicinal product shall contain information confirming compliance with the Guidelines for the preclinical and clinical development of combination medicinal products (Appendix to the Recommendation of the Collegium of the Eurasian Economic Commission No. 25 dated September 2, 2019);

2.34. copies of reports on comparative pharmacokinetic and (or) comparative pharmacodynamic and (or) comparative clinical studies (trials) and reports on biopharmaceutical studies for generic medicinal products, hybrid medicinal products carried out in accordance with Good Clinical Practice shall be submitted during State Registration of a medicinal product (if bioequivalence (bioavailability) study (test) is not applicable). The specified copies of the reports shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and submitted in electronic form in Belarusian, Russian or English.

Synopsis and a brief description of a biopharmaceutical study (sections of these reports), drawn up in a foreign language, shall be submitted on paper, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer).

A copy of the report on the conducted pharmacodynamic or Clinical Trials shall contain information confirming the conduct of trials in accordance with Appendices No. 2 or No. 3 to the Rules for Conducting Bioequivalence Studies. This report shall be drawn up in accordance with Appendix No. 1 to the Rules of Good Clinical Practice of the Eurasian Economic Union, approved by the Resolution of the Council of the Eurasian Economic Commission No. 79 dated November 3, 2016.

For hybrid medicinal products, copies of reports shall be submitted in accordance with Clause 7 of the special requirements for the modules of the master file of a medicinal product of Appendix No. 1 to the Rules for the Registration and Examination of Medicines.

For liposomal medicinal products for intravenous administration, copies of reports shall be submitted in accordance with the Guidelines for the Pharmacokinetic and Clinical Trial of bioequivalence of liposomal medicinal products for intravenous administration, approved by the Resolution of the Collegium of the Eurasian Economic Commission No. 111 dated September 15, 2020.

For block copolymer micellar medicinal products, copies of reports shall be submitted in accordance with Appendix No. 1 to the Recommendation of the Collegium of the Eurasian Economic Commission No. 15 dated September 15, 2020 "On guidelines for assessing the quality and studying bioequivalence of certain groups of medicinal products".

For medicinal products for parenteral administration, coated with nanoparticles, and medicinal products based on colloidal iron for intravenous administration, copies of reports shall be submitted in accordance with Appendix No. 2 to the Recommendation of the Collegium of the Eurasian Economic Commission No. 15 dated September 15, 2020 "On guidelines for assessing the quality and studying bioequivalence of certain groups of medicinal products".

For medicinal products for inhalation and nasal medicinal products, copies of reports shall be submitted in accordance with the Guidelines for the preparation of clinical documentation (conducting clinical trials, confirmation of therapeutic equivalence) for medicinal products for inhalation used for the treatment of bronchial asthma in adults, adolescents and children and chronic obstructive lung disease in adults (Appendix to the Recommendation of the Collegium of the Eurasian Economic Commission No. 1 dated January 14, 2020).

For medicinal products with modified release, the active substance of which is registered in the composition of the medicinal product with a different release rate, copies of reports shall be

submitted in accordance with the requirements of the Rules for Conducting Bioequivalence Studies.

For topical corticosteroid medicinal products, copies of reports shall be submitted in accordance with the Rules for Conducting Bioequivalence Studies;

2.35. copies of reports on comparative preclinical (nonclinical) studies of a medicinal product and on comparative Clinical Trials or (pharmacokinetic (pharmacodynamic) studies or immunogenic tests) conducted in accordance with Good Clinical Practice to confirm comparability with the original (reference) medicinal product shall be submitted during State Registration of a biosimilar medicinal product in electronic form in Belarusian, Russian or English and certified by the Holder of the Registration Certificate (Applicant, Manufacturer). These reports shall contain information confirming the conduct of studies in accordance with Clause 10 of special requirements for the modules of the master file of a medicinal product of Appendix No. 1 to the Rules for the Registration and Examination of Medicines and the Rules for conducting research on biological medicinal products of the Eurasian Economic Union, approved by the Resolution of the Council of the Eurasian Economic Commission No. 89 dated November 3, 2016.

A brief description of the preclinical (nonclinical) study of the medicinal product and Synopsis (sections of reports) drawn up in a foreign language shall be submitted on paper, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer);

2.36. reviews of preclinical and clinical data, information on the experience of using a medicinal product (scientific articles, monographs, publications, clinical protocols, methodological guidelines) shall be submitted during State Registration, conditional State Registration of a medicinal product, during confirmation of State Registration (not submitted for a medicinal product from medicinal plant raw materials) in electronic form in Belarusian, Russian or English. Reviews of preclinical and clinical data compiled in a foreign language shall be accompanied by the translations into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer).

For original medicinal products, reviews of preclinical and clinical data shall be submitted with the attachment of a summary of preclinical (nonclinical) studies and a summary of clinical data in accordance with Clause 2 of the Requirements for the documents of the master file given in module 2, Appendix No. 1 to the Rules for the Registration and Examination of Medicines.

For a medicinal product, the active substance of which has been well studied in medical practice (its effectiveness and an acceptable level of safety are recognized, which was confirmed by materials on clinical and epidemiological trials and published in peer-reviewed scientific medical publications, and its first use in the Republic of Belarus was more than 12 years ago), reviews of preclinical and clinical data with detailed information from the peer-reviewed scientific bibliography, which reflects the experience of use and the results of evaluating the efficacy, safety as well as benefit-risk ratio of the medicinal product shall be submitted. Medicinal products, the active substance of which is well studied in medical practice, include medicinal products from raw materials of natural origin, vitamins and vitamin-mineral complexes, antiseptic solutions, water for injection, adsorbents, carminative medicinal products, medicines from the group of irritating and enveloping agents.

For a homeopathic medicinal product without declared indications for medical use, reviews of preclinical and clinical data shall be submitted, while the conditions specified in Clause 14 of the special requirements for documents of the master file of certain types of medicinal products of Appendix No. 1 to the Rules for Registration and Examination of medicinal products shall be observed;

2.37. a copy of the master file of the pharmacovigilance system of the Holder of the Registration Certificate (or a brief description out of the pharmacovigilance system if the Republican Unitary Enterprise "Center for Expertise and Testing in Healthcare" has a valid version of the master file of the pharmacovigilance system) shall be submitted during State Registration,

conditional State Registration of a medicinal product in electronic form in Belarusian, Russian or English and shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer).

A copy of the master file of the pharmacovigilance system of the Holder of the Registration Certificate shall be submitted when the Holder of the Registration Certificate first submits an application for State Registration, conditional State Registration of a medicinal product.

A brief description out of the pharmacovigilance system, drawn up in a foreign language, shall be presented on paper, certified by the Holder of the Registration Certificate and accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate.

These documents shall comply with the requirements of the Rules of Good Pharmacovigilance Practice of the Eurasian Economic Union, approved by the Resolution of the Council of the Eurasian Economic Commission No. 87 dated November 3, 2016 (hereinafter referred to as the Rules of Good Pharmacovigilance Practice);

2.38. a risk management plan for a medicinal product shall be submitted during State Registration, conditional State Registration of a medicinal product, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) in electronic form in Belarusian, Russian or English.

The specified document shall comply with the requirements of the Rules of Good Pharmacovigilance Practice.

The part of the risk management plan for a medicinal product containing a summary and attached materials on additional risk minimization measures, drawn up in a foreign language, shall be submitted on paper, certified by the Holder of the Registration Certificate and accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate;

2.39. a copy of the periodically updated safety report of the medicinal product shall be submitted during confirmation of State Registration, confirmation of conditional State Registration of a medicinal product (not submitted for a medicinal product made from medicinal plant materials) in electronic form in Belarusian, Russian or English and certified by the Holder of the Registration Certificate (Applicant, Manufacturer). Sections of the periodically updated safety report of the medicinal product, including a summary of the periodically updated safety report, an integrated analysis of the benefit-risk ratio for approved indications for medical use and the conclusion of a periodically updated safety report, drawn up in a foreign language, shall be presented on paper, certified by the Holder of the Registration Certificate and accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate.

The specified document shall comply with the requirements of the Rules of Good Pharmacovigilance Practice;

2.40. the justification of the Holder of the Registration Certificate on the compliance of the medicinal product with the requirements for the application of the conditional State Registration procedure shall be submitted during conditional State Registration of the medicinal product and shall contain:

an overview of the methods of providing medical care for the treatment, medical prevention or diagnosis of the disease for which the medicinal product is intended, with a quantitative assessment of the unmet medical need;

the results of completed Clinical Trials of the medicinal product, information on ongoing Clinical Trials with an assessment of the possibility of their completion and obtaining complete Clinical data on the medicinal product;

an assessment of the benefits for patients in the case of the use of a medicinal product, indicating the degree of satisfaction of the unmet medical need;

assessment of the risks for patients associated with the lack of complete Clinical data on the medicinal product;

an assessment of the “benefit-risk” ratio of a medicinal product, confirming that the benefit to the patient or public health due to conditional State Registration and the availability of the

medicinal product outweighs the risk associated with the lack of complete Clinical data on the medicinal product;

2.41. a copy of the report with the submission of documentary evidence on the fulfillment of the obligations established during the conditional State Registration shall be submitted during confirmation of the conditional State Registration, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall include:

a chronological list of obligations established during conditional State Registration, the results of their implementation or available data on the progress of their fulfillment;

an assessment of the “benefit - risk” ratio of a medicinal product based on data obtained in fulfilling established obligations, as well as data on safety and efficiency after conditional State Registration;

new preclinical or pharmaceutical data (if any);

interim report on the Clinical Trial of the medicinal product;

the closing report on the Clinical Trial shall be submitted in accordance with Appendix 1 to the Rules of Good Clinical Practice of the Eurasian Economic Union, approved by the Decision of the Council of the Eurasian Economic Commission No. 79 dated November 3, 2016;

2.42. a Manufacturer's declaration containing data on the assessment of the risk to the environment in relation to medicinal products containing genetically modified components shall be submitted during State Registration, conditional State Registration of the medicinal product and shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer). The document drawn up in a foreign language shall be accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer).

3. Documents constituting the master file submitted for State Registration of a pharmaceutical substance:

3.1. the application shall be prepared in the form according to Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.1 "State registration and obtaining a registration certificate for a medicinal product or pharmaceutical substance";

3.2. information on the development submitted during the registration of a new pharmaceutical substance or pharmaceutical substance for the production of biological medicinal products shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall contain information on the pharmaceutical substance, in terms of completeness and volume, corresponding to the information on the pharmaceutical substance submitted in the pharmaceutical development of the medicinal product, as well as information on the medicinal product itself, planned for manufacture using this pharmaceutical substance (information on the composition, development of the dosage form and the manufacturing process, physicochemical and biological properties);

3.3. Copies of reports on physical, chemical and biological tests to confirm compatibility with the original (reference) medicinal product shall be submitted during State Registration of the pharmaceutical substance used for the production of a biosimilar medicinal product, certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall comply with the requirements of Sub-clause 2.21 of Clause 2 of these Instructions;

3.4. copies of Manufacturer's documents, including a description of the manufacturing process of a pharmaceutical substance, a concise manufacturing process (Synthesis) scheme, information on the size of the industrial batch, methods for confirming the structure, justification of impurities, a manufacturing process validation plan and a guarantee obligation to provide a manufacturing process validation report, or a manufacturing process validation report, a report on the validation of quality control methods or a CEP certificate (if any). The specified copies of documents shall be submitted during the State Registration of pharmaceutical substances of domestic manufacture, shall be certified by the Holder of the Registration Certificate (Applicant,

Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall comply with the requirements of Sub-clause 2.15 of Clause 2 of these Instructions.

Copies of documents including a manufacturing process validation plan and a guarantee obligation to provide a manufacturing process validation report shall contain information confirming that the manufacturing process validation will be performed on the first three industrial batches;

3.5. copies of the Manufacturer's documents, including a description of the pharmaceutical substance manufacturing process, a concise manufacturing process (Synthesis) scheme, information on the size of the industrial batch, methods for confirming the structure, justification of impurities, a declaration on the validation of the manufacturing process, a report on the validation of quality control methods or a CEP certificate (if availability), shall be submitted during the State Registration of pharmaceutical substances of foreign manufacture, certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and shall comply with the requirements of Sub-clause 2.15 of Clause 2 of these Instructions.

A copy of the document, including the declaration on the validation of the manufacturing process, in the case of State Registration of a pharmaceutical substance of foreign manufacture at the request of a legal entity of the Republic of Belarus that has a special permit (license) to carry out pharmaceutical activities, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.15 of Clause 2 of these Instructions.

A copy of the document containing the declaration on the validation of the manufacturing process, in the case of State Registration of a pharmaceutical substance at the request of a foreign manufacturer, shall be accompanied by information on the validation of the manufacturing process;

3.6. The draft normative document on quality shall be prepared in Belarusian or Russian and include the following sections: title page, introductory part, definition, specification, description of test methods.

The title page shall be drawn up in the form according to Appendix 5.

The section "Introductory part" shall contain: the name of the pharmaceutical substance in Belarusian or Russian, Latin and English, structural and empirical formulas, molecular weight, as well as information on the purpose of the pharmaceutical substance (for the manufacture of which medicinal products it is used, for example, for medicinal products for external use, for parenteral medicinal products, etc.).

The section "Definition" shall contain: the chemical name of the pharmaceutical substance and, if necessary, information on the presence of excipients (for example, stabilizers). For substances of plant origin (for example, dry extracts, essential oils, etc.), the name and used part of the producing plant shall be indicated.

The "Specification" section shall be presented in the form of a table consisting of 3 columns: quality indicators, norms (permissible limits), links to test methods.

The names of quality indicators in the specification, their sequence shall be indicated in accordance with the State Pharmacopoeia of the Republic of Belarus. Quality indicators and norms (permissible limits) shall be indicated in accordance with the requirements of the general pharmacopoeial monographs of the State Pharmacopoeia of the Republic of Belarus, and if absent in it, in accordance with the requirements of the general pharmacopoeial monographs of the European Pharmacopoeia, the Pharmacopoeia of the Eurasian Economic Union.

In the section "Description of Test Methods", the test methods for the quality indicators of a pharmaceutical substance specified in the specification (with links to the methods of the State Pharmacopoeia of the Republic of Belarus) shall be given in accordance with the principles of formalizing general and particular pharmacopoeial monographs of the State Pharmacopoeia of the Republic of Belarus. The section "Description of test methods" shall include subsections:

"description (properties)", "authenticity (identification)", "trials", "quantitative determination", "impurities".

When describing quality control procedures, after the section heading, shall be indicated:

a link to a section, general or particular pharmacopoeial monograph or page of the State Pharmacopoeia of the Republic of Belarus in accordance with the method used;

norm (permissible limits);

equipment used (if necessary);

list of reference materials and their qualifications;

methods for the preparation of reagents and (or) solutions, if they are not described in the State Pharmacopoeia of the Republic of Belarus;

trial method.

When carrying out trials by methods providing for obtaining spectra, chromatograms, electrophoregrams, etc. their samples shall be attached to the draft normative document on quality.

If the State Pharmacopoeia of the Republic of Belarus contains descriptions of the characteristics of reagents, standard solutions, buffer solutions and materials used in testing, their names shall be italicized and marked by the symbol "P". If the State Pharmacopoeia of the Republic of Belarus does not contain descriptions of the characteristics of reagents, standard solutions, buffer solutions and materials used, it shall be necessary to indicate their designations, qualifications and (or) the Manufacturer's documents regulating their quality, indicating the name. The names of titrated solutions described in the State Pharmacopoeia of the Republic of Belarus shall also be italicized, without the symbol “P”. When reference materials are used in testing, their qualification and Manufacturer's name or a reference to the corresponding pharmacopoeia shall be indicated.

Calculation formulas shall be presented in expanded and abbreviated forms and accompanied by an explanation of the physical values indicated in them. The designations of physical values shall be given in accordance with the requirements of the State Pharmacopoeia of the Republic of Belarus. Carrying-over part of the calculation formula to another line shall not be allowed.

To measure the physical values specified in the normative document on quality, the units of measurement provided by the International System of Units (SI system) and the units of measurement used on an equal basis with them shall be used.

Requirements for individual sections of the normative document on quality:

in the "Description (Properties)" section, the following characteristics of the physical state of the pharmaceutical substance shall be indicated: liquid, micro-capsules, granules, powder (amorphous, fine-crystalline, crystalline) and color. The solubility of a pharmaceutical substance shall be indicated in accordance with the terms of section 1.4 of the State Pharmacopoeia of the Republic of Belarus. To characterize the solubility, solvents that cover a wide scale of polarity (for example: water, alcohol 96%, acetone, hexane) shall be used.

Color shall be described as: white, blue, green, yellow, orange, red, etc. The permissible color range for pharmaceutical substances shall be within the tone range. In case of color tones, the color contained in the least shall be indicated in the first place, the predominant color shall be indicated with a hyphen (for example, "crystalline powder of green with a brownish tone of color or brownish-green"). For lightly colored samples, the name of the color shall be characterized by the suffix "-ish" or indicated "light-". For example, "yellowish" or "light yellow".

The smell shall be characterized by the terms: "odorless", "with a characteristic odor", "with a faint odor".

If necessary, information shall be provided on absorbability, on possible changes during storage in air, in the light (color change, etc.);

the section "Related impurities" shall be mandatory for inclusion in the normative document on quality, and cases of its non-inclusion in the normative document on quality shall be justified. The "Related Impurities" section shall include the determination of the content of each specified impurity, unspecified impurities and the sum of impurities. The "Impurities" section shall contain the list of the structural formulas and chemical names of the specified and other detectable impurities. When chromatographic methods are used for these purposes, the type of sorbent, the

composition of the mobile phase solution, the amount of the testing (introduced or applied) substance, the amount of the reference standard, the chromatographic time, the reagents used for development, and all other conditions determining the chromatography process shall be indicated. When using liquid or gas chromatography, the relative retention times of all determined components and the limits of integration shall be indicated. The method of checking the suitability of the chromatographic system shall also be indicated;

the section "Residual quantities of organic solvents" shall be included in the normative document on quality in accordance with the approaches given in the general pharmacopoeial monograph of the State Pharmacopoeia of the Republic of Belarus "5.4. Residual quantities of organic solvents";

in the section "Microbiological purity" the presence (absence) of antimicrobial action, a description of sample preparation, indicating the amount of sample and diluent (for each dilution) shall be indicated. If a membrane filtration method is used, the amount of flushing liquid shall be indicated. A brief description of the method and conditions of inoculation of medium shall be indicated;

in the sections "Abnormal toxicity", "Pyrogenicity". "Content of substances of histamine-like action", the test doses, route of administration, observation period shall be indicated;

the section "Bacterial endotoxins" shall indicate the presence (absence) of interfering factors, concentration in the initial solution (preparation conditions, if necessary);

the section "Sterility" shall provide a summary of the methods (direct inoculation or membrane filtration);

in the section "Quantitative determination" the following shall be indicated: the percentage in terms of anhydrous or dry substance or substance "as-is" or the content in 1 milligram of the substance, in micrograms (μg/mg) or the activity of 1 milligram of the substance, in units of action (U/mg) or in other units (ATE, ME, and others) in accordance with the State Pharmacopoeia of the Republic of Belarus; description of the method for quantitative determination of the substance.

Detailed requirements and criteria applicable to universal and specific testing of pharmaceutical substances shall be set out in the draft normative document on quality in accordance with Appendix No. 1 to the Guidelines for drawing up a regulatory document on the quality of a medicinal product, approved by the Resolution of the Collegium of the Eurasian Economic Commission No. 151 dated September 7, 2018.

The text of the normative document on quality shall be short, without repetitions and exclude the possibility of double interpretation. Abbreviations of words in the text, names of figures and diagrams shall not be allowed, with the exception of abbreviations contained in the specification and established by the State Pharmacopoeia of the Republic of Belarus.

Requirements for the quality of the pharmaceutical substance shall be stated in the imperative form, and the test methods - in the third person plural.

If the method and (or) the test procedure specified in the normative document on quality are described in the general pharmacopoeia monograph of the State Pharmacopoeia of the Republic of Belarus or the Pharmacopoeia of the Eurasian Economic Union, a reference to the source shall be indicated without a description of the method and (or) test procedure, indicating, if necessary, sample preparation. When the methods described in the pharmacopoeias of other states are included, a complete description of the methods and (or) test methods used shall be included in the normative document on quality.

Terms, designations and definitions shall comply with the State Pharmacopoeia of the Republic of Belarus. When using terms and designations that are defined by the pharmacopoeias of other states and are not generally recognized, their definitions shall be given in the text.

In the text it shall be not allowed to use:

colloquial speech;

various terms that are close in meaning (synonyms) for the same concept, as well as foreign words and terms in the presence of equivalent words and terms in the Russian language;

abbreviations of units of measurement, if they are used without numbers;

replacing of words with letter symbols (except for tables and formulas);

mathematical signs without numbers.

The text of the normative document on quality shall be drawn up as follows:

one-sided printing;

margin sizes: left - 30 mm, right - 15 mm, top and bottom - 20 mm;

paragraph indentation - 12.5 mm;

Times New Roman font, size 14 (for the number of the normative document on quality - 16);

the titles and name of the pharmaceutical substance shall begin with a capital letter and be in bold;

the main text shall be printed at 1.5 line spacing, text in specifications and notes - at 1 line spacing, text in headings - at 1 line spacing;

the pages of the normative document on quality shall be numbered;

figures, flow charts, diagrams, graphs, spectra and chromatograms may be presented on separate pages or given in the text of the normative document on quality.

Inclusion of sections "Storage", "Packaging" and "Expiration date or the time frame for the re-examination", "Labeling" shall not be required. Information on storage conditions, packaging and expiration date or the time frame for the re-examination of the pharmaceutical substance shall be submitted in the application for State Registration;

3.7. a copy of the Manufacturer's document confirming the quality of one batch of a pharmaceutical substance shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.26 of Clause 2 of these Instructions;

3.8. copies of documents confirming the quality of reference materials used in quality control of a pharmaceutical substance shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.27 of Clause 2 of these Instructions;

3.9. copies of documents on quality control of primary packaging materials (primary packaging components) and documents confirming that primary packaging materials (primary packaging components) are suitable for use for packaging pharmaceutical substances, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.17 of Clause 2 of these Instructions;

3.10. copies of documents confirming the quality of one batch of primary packaging materials (primary packaging components) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.29 of Clause 2 of these Instructions;

3.11. copies of the Manufacturer's documents containing the results of the stability study of the pharmaceutical substance (plan, report, tables with research results) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer), accompanied by a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.18 of Clause 2 of these Instructions;

3.12. the original or a copy of the document confirming the registration of a pharmaceutical substance in the country of manufacture, if it is necessary to register it in accordance with the requirements of the legislation of the country of manufacture, shall be submitted during State Registration of pharmaceutical substances of foreign manufacture with a translation into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). A copy of the document shall be notarized. Documents shall be

legalized and apostilled, unless otherwise provided by international treaties of the Republic of Belarus;

3.13. a copy of the license issued by the authorized body of the country of manufacture and granting the right to manufacture the medicinal product shall be submitted during State Registration of pharmaceutical substances of foreign manufacture with a translation into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). A copy of the document shall be notarized. Documents shall be legalized and apostilled, unless otherwise provided by international treaties of the Republic of Belarus;

3.14. a copy of the document certifying the manufacture of a pharmaceutical substance under the conditions of Good Manufacturing Practice, issued by the authorized body of the country of manufacture of the pharmaceutical substance (for each participant in the manufacture of a pharmaceutical substance). If there is no information in this document about the date of the recent inspection of the specified production, its validity period shall deem to be not more than 3 years from the date of its issue. Submitted during State Registration of pharmaceutical substances of foreign manufacture. Documents shall be accompanied by a translation into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). A copy of the document shall be notarized. Documents shall be legalized and apostilled, unless otherwise provided by international treaties of the Republic of Belarus;

3.15. the original or a copy of the document confirming that a legal entity of the Republic of Belarus, an individual entrepreneur registered in the Republic of Belarus, a foreign legal entity, a foreign organization created in accordance with the legislation of foreign states are the official representative of the Holder of the Registration Certificate for a pharmaceutical substance, shall be submitted with a translation into Belarusian or Russian, certified by the Holder of the Registration Certificate (Applicant, Manufacturer). A copy of the document shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer).

4. The documents making up the master file for making amendments to the master file for a medicinal product (except for the medicinal products specified in Clause 5 of these Instructions) shall meet the following requirements:

4.1. when introducing a new indication and (or) a new method of application (administration) into the SmPC, Basic Prescribing Information (package leaflet):

4.1.1. the application shall be prepared in the form according to Appendix 1 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file", approved by the Resolution of the Ministry of Health of the Republic of Belarus No. 42 dated May 12, 2022;

4.1.2. the justification for the amendment, indicating the sections of the SmPC and the Basic Prescribing Information (package leaflet), which are amended, shall be presented in the form of a table "old edition and new edition";

4.1.3. the draft SmPC shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.1.4. the draft Basic Prescribing Information (package leaflet) shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.1.5. copies of reports on preclinical (nonclinical) studies of a medicinal product (if necessary) and clinical studies (trials) of a medicinal product for a new indication for medical use or a new method of application (administration) in accordance with Good Clinical Practice (except for a generic medicinal product) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.31 and 2.32 of Clause 2 of these Instructions;

4.1.6. the risk management plan for the medicinal product shall comply with the requirements of Sub-clause 2.38 of Clause 2 of these Instructions;

4.2. upon exclusion from the SmPC, Basic Prescribing Information (package leaflet), previously provided indications for medical use and (or) method of application (administration):

4.2.1. the application shall be prepared in the form according to Appendix 1 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.2.2. the justification for the amendment, indicating the sections of the SmPC and the Basic Prescribing Information (package leaflet), which are amended, shall be presented in the form of a table "old edition and new edition";

4.2.3. the draft SmPC shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.2.4. the draft Basic Prescribing Information (package leaflet) shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.2.5. the Manufacturer's document confirming the need to exclude the previously provided indications for medical use and (or) the method of application (administration) shall contain information on the reasons for the amendments: identified adverse reactions, the results of medical use and (or) clinical trials, the decision of the authorized body of the country of manufacture, or the country of the Holder of the Registration Certificate on the exclusion from the SmPC or Basic Prescribing Information (package leaflet) of any indications for medical use, the method of application (administration) declared earlier, other information about the medicinal product;

4.3. when making amendments to sections of the SmPC, Basic Prescribing Information (package leaflet), including pharmacological and clinical sections:

4.3.1. the application shall be prepared in the form according to Appendix 1 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.3.2. the justification for the amendment, indicating the sections of the SmPC and the Basic Prescribing Information (package leaflet), which are amended, shall be presented in the form of a table "old edition and new edition";

4.3.3. the draft SmPC shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.3.4. the draft Basic Prescribing Information (package leaflet) shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.4. when making amendments to the composition of a medicinal product (replacement or introduction of an additional manufacturer of a pharmaceutical substance, introduction, exclusion or replacement of excipients):

4.4.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.4.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition" (if the amendment affects the SmPC and the Basic Prescribing Information (package leaflet), registration of amendments into these documents in the form of a table "old edition and new edition" shall be essential);

4.4.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.4.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.4.5. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

4.4.6. copies of Manufacturer's documents, including a description of the pharmaceutical substance manufacturing process, a concise manufacturing process (Synthesis) scheme,

information on the size of the industrial batch, methods for confirming the structure, justification of impurities, a declaration of the manufacturing process validation or a CEP certificate (if any) and a report on the validation of control methods quality, in case of replacement or introduction of an additional manufacturer of a pharmaceutical substance that is a part of a medicinal product, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.15 of Clause 2 of these Instructions;

4.4.7. copies of documents on quality control of the pharmaceutical substance and excipients, if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.16 and 2.23 of Clause 2 of these Instructions;

4.4.8. copies of the Manufacturer's documents containing the results of the stability study of the pharmaceutical substance (plan, report, tables with research results), in the event of replacement or introduction of an additional manufacturer of the pharmaceutical substance that is part of the medicinal product, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.18 of Clause 2 of these Instructions;

4.4.9. Manufacturer's document containing information on the composition of the medicinal product, indicating the amount of all ingredients, including all excipients per dosage unit (for dosed medicinal products) or unit of mass or volume (for non-dosed medicinal products) with reference to the documents on quality control of the pharmaceutical substances and excipients, shall comply with the requirements of Sub-clause 2.19 of Clause 2 of these Instructions;

4.4.10. copies of the Manufacturer's documents, including a description of the new manufacturing process of the medicinal product, quality control of intermediate products, a concise manufacturing scheme, batch formula, volume of the industrial batch, a report on the validation of the manufacturing process, if the change in the composition entails a change in the manufacturing process, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.22 of Clause 2 of these Instructions;

4.4.11. a draft on amending the normative document on quality, if the amendments made affect this section of the master file, shall be prepared in the form in accordance with Appendix 7.

In the event that the amendments in total affect more than half of the text of the normative document on quality or if there are more than three amendments, the normative document on quality in a new edition shall be submitted;

4.4.12. copies of reports on validation of medicinal product quality control methods, if the amendments introduced affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.25 of Clause 2 of these Instructions;

4.4.13. copies of the Manufacturer's documents confirming the quality of one batch of the medicinal product and (or) excipients shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.26 of Clause 2 of these Instructions;

4.4.14. copies of the Manufacturer's documents containing the results of the stability study of the medicinal product (plan, report, tables with the research results), if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.18 and 2.30 of Clause 2 of these Instructions;

4.4.15. copies of reports on the results of a comparative study of the bioavailability of a medicinal product with a new and previously registered composition shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.33 and 2.34 of Clause 2 of these Instructions. In case of a change in a previously registered composition that may affect bioavailability, in vivo bioequivalence studies shall be carried out, unless other justification is provided;

4.5. when making amendments to the "Composition" section of the master file for a medicinal product (if the amendments do not affect the actual composition of the medicinal product):

4.5.1. the application shall be prepared in the form according to Appendix 1 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.5.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition" (if the amendment affects the SmPC and the Basic Prescribing Information (package leaflet), registration of amendments into these documents in the form of a table "old edition and new edition" shall be essential);

4.5.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.5.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.5.5. Manufacturer's document containing information on the composition of the medicinal product, indicating the amount of all ingredients, including all excipients per dosage unit (for dosed medicinal products) or unit of mass or volume (for non-dosed medicinal products) with reference to the up-to-date documents on quality control of the pharmaceutical substances and excipients, shall comply with the requirements of Sub-clause 2.19 of Clause 2 of these Instructions;

4.5.6. a draft on amending the normative document on quality, if the amendments made affect this section of the master file, shall be prepared the form in accordance with Appendix 7.

In the event that the amendments in total affect more than half of the text of the normative document on quality or if there are more than three amendments, the normative document on quality in a new edition shall be submitted;

4.5.7. copies of the Manufacturer's documents confirming the quality of one batch of a medicinal product and (or) pharmaceutical substance and (or) excipients, if the amendments made affect these sections of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.26 of Clause 2 of these Instructions;

4.6. when making amendments to the normative document on quality (including, if there are documents of the manufacturer of a pharmaceutical substance in the master file for a medicinal product that contains this pharmaceutical substance) in case of a change in quality indicators, control methods, test methods:

4.6.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.6.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition" (if the amendment affects the SmPC and the Basic Prescribing Information (package leaflet), registration of amendments into these documents in the form of a table "old edition and new edition" shall be essential);

4.6.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.6.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.6.5. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, if the

amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

4.6.6. the draft on amendments to the normative document on quality shall be prepared in the form according to Appendix 7.

In the event that the amendments in total affect more than half of the text of the normative document on quality or if there are more than three amendments, the normative document on quality in a new edition shall be submitted.

When making amendments to the document on quality control of a pharmaceutical substance (if there are documents of the manufacturer of the pharmaceutical substance in the master file for a medicinal product, which contains this pharmaceutical substance), no requirements shall be imposed;

4.6.7. copies of reports on validation of medicinal product quality control methods, if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.15.7 and 2.25 of Clause 2 of these Instructions;

4.6.8. a copy of the Manufacturer's document confirming the quality of one batch of a medicinal product shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.26 of Clause 2 of these Instructions;

4.6.9. copies of documents confirming the quality of reference materials used in quality control of a medicinal product (if the amendments made affect this section of the master file) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.27 of Clause 2 of these Instructions;

4.7. when changing the shelf life of a medicinal product (including in the case of the presence of documents of the manufacturer of a pharmaceutical substance in the master file for a medicinal product, which contains this pharmaceutical substance):

4.7.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.7.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition" (if the amendment affects the SmPC and the Basic Prescribing Information (package leaflet), registration of amendments into these documents in the form of a table "old edition and new edition" shall be essential);

4.7.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.7.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.7.5. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

4.7.6. a copy of the Manufacturer's document confirming the quality of one batch of a medicinal product shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.26 of Clause 2 of these Instructions;

4.7.7. copies of the Manufacturer's documents containing the results of the stability study of the medicinal product (plan, report, tables with research results) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.18 and 2.30 of Clause 2 of these Instructions;

4.8. when changing the storage conditions of the medicinal product (including in the case of the presence of documents of the manufacturer of a pharmaceutical substance in the master file for a medicinal product, which contains this pharmaceutical substance):

4.8.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.8.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition" (if the amendment affects the SmPC and the Basic Prescribing Information (package leaflet), registration of amendments into these documents in the form of a table "old edition and new edition" shall be essential);

4.8.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.8.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.8.5. models of primary and secondary packaging (intermediate packaging - if any) shall be submitted in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian and comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

4.8.6. a copy of the Manufacturer's document confirming the quality of one batch of a medicinal product, if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.26 of Clause 2 of these Instructions;

4.8.7. copies of the Manufacturer's documents containing the results of the stability study of the medicinal product under new storage conditions (plan, report, tables with research results) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.18 and 2.30 of Clause 2 of these Instructions;

4.9. when submitting an updated draft normative document on quality (including, if there are documents of the manufacturer of a pharmaceutical substance in the master file for a medicinal product that contains this pharmaceutical substance) in case of a change in quality indicators, control methods, test methods:

4.9.1. the application shall be executed in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.9.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition" (if the amendment affects the SmPC and the Basic Prescribing Information (package leaflet), registration of amendments into these documents in the form of a table "old edition and new edition" shall be essential);

4.9.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.9.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.9.5. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

4.9.6. the draft updated normative document on quality shall comply with the requirements of Sub-clause 2.24 of Clause 2 and Sub-clause 3.6 of Clause 3 of these Instructions.

For a pharmaceutical substance when making amendments to the document on quality (if there are documents of the manufacturer of the pharmaceutical substance in the master file for a medicinal product, which contains this pharmaceutical substance), no requirements shall be imposed;

4.9.7. copies of reports on validation of medicinal product quality control methods, if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.15.7 and 2.25 of Clause 2 of these Instructions;

4.9.8. a copy of the Manufacturer's document confirming the quality of one batch of the medicinal product shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.26 of Clause 2 of these Instructions;

4.9.9. copies of documents confirming the quality of reference materials used in quality control of a medicinal product (if the amendments made affect this section of the master file) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.27 of Clause 2 of these Instructions;

4.10. when changing the material, type of primary packaging, components for packaging a medicinal product (including if there are documents of the manufacturer of a pharmaceutical substance in the master file for a medicinal product, which includes this pharmaceutical substance), changing the packaging of bulk product:

4.10.1. the application shall be executed in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.10.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition" (if the amendment affects the SmPC and the Basic Prescribing Information (package leaflet), registration of amendments into these documents in the form of a table "old edition and new edition" shall be essential);

4.10.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.10.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.10.5. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

4.10.6. copies of documents on quality control of new packaging materials (new packaging components, new primary packaging components) and documents confirming that new primary packaging materials (new packaging components, new primary packaging components) of the medicinal product and (or) bulk product are suitable for packaging, contact with medicinal products, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.17 and 2.28 of Clause 2 of these Instructions;

4.10.7. copies of documents confirming the quality of one series of new primary packaging materials (new packaging components, new primary packaging components) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.29 of Clause 2 of these Instructions;

4.10.8. copies of the Manufacturer's documents containing the results of the stability study of the medicinal product and (or) bulk product in packaging made of a new material or a new type of primary packaging (plan, report, tables with the research results), if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate

(Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.18 and 2.30 of Clause 2 of these Instructions;

4.11. when making changes to the manufacturing process of a medicinal product (including if there are documents of the manufacturer of a pharmaceutical substance in the master file for a medicinal product, which contains this pharmaceutical substance):

4.11.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.11.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition";

4.11.3. copies of reports on physicochemical and biological studies to confirm the comparability of a medicinal product manufactured using a new and previously approved manufacturing processes - for a biotechnological medicinal product, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and submitted in accordance with the Rules for Conducting Research on Biological Medicines of The Eurasian Economic Union, approved by the Resolution of the Council of the Eurasian Economic Commission No. 89 dated November 3, 2016;

4.11.4. copies of Manufacturer's documents, including a description of the new manufacturing process of a pharmaceutical substance with justification for the amendments, a concise manufacturing scheme, the size of the industrial batch, methods of confirming the structure, justification of impurities, a manufacturing process validation report or a CEP certificate (if any), if the changes affect these sections of the master file - when making changes to the manufacturing process of a pharmaceutical substance of domestic or foreign manufacture, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 3.4 and 3.5 of Clause 3 of these Instructions;

4.11.5 copies of Manufacturer's documents, including a description of the new manufacturing process of a pharmaceutical substance with justification for the amendments, a concise manufacturing scheme, the size of the industrial batch, methods of confirming the structure, justification of impurities, a manufacturing process validation report or a CEP certificate (if any), if the changes affect these sections of the master file - when making changes to the manufacturing process of a pharmaceutical substance, and the presence of documents of the Manufacturer of the pharmaceutical substance in the master file for a medicinal product, which contains this pharmaceutical substance, or when making changes to the manufacturing process of a pharmaceutical substance of foreign manufacture, registered at the request of a legal entity of the Republic of Belarus with a special permit (license) to carry out pharmaceutical activities, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.15 of Clause 2 of these Instructions;

4.11.6. copies of the Manufacturer's documents, including a new description of the manufacturing process of the medicinal product, quality control of intermediate products, a concise manufacturing scheme, batch formula, the volume of an industrial batch, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.22 of Clause 2 of these Instructions;

4.11.7. a copy of the report on the validation of the new manufacturing process of the medicinal product, if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.22 of Clause 2 of these Instructions;

4.11.8. a copy of the Manufacturer's document confirming the quality of one batch of the medicinal product shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.26 of Clause 2 of these Instructions;

4.11.9. copies of the Manufacturer's documents containing the results of the stability study of the medicinal product manufactured using a new manufacturing process (plan, report, tables with research results) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.18 and 2.30 of Clause 2 of these Instructions;

4.11.10. copies of reports on preclinical (nonclinical) studies and clinical studies (trials) to confirm the comparability of a medicinal product manufactured using a new and previously approved manufacturing processes (in the absence of convincing evidence of comparability based on reports on physicochemical and biological studies), - for biotechnological medicinal product, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and submitted in accordance with the Rules for research of biological medicinal products of the Eurasian Economic Union, approved by the Resolution of the Council of the Eurasian Economic Commission No. 89 dated November 3, 2016;

4.11.11. Copies of reports on the results of a comparative study of the bioavailability of a medicinal product manufactured using a new and previously approved manufacturing processes (except for a biotechnological medicinal product) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.33 and 2.34 of Clause 2 of these Instructions. In case of a change in a previously approved manufacturing process, that may affect the bioavailability, in vivo bioequivalence studies shall be carried out, unless other justification is provided;

4.11.12. the risk management plan for the biotechnological medicinal product shall comply with the requirements of Sub-clause 2.38 of Clause 2 of these Instructions;

4.12. when making changes to the design of the models of the primary and (or) secondary, and (or) intermediate packaging of the medicinal product (if any) or the introduction of additional models of the primary and (or) secondary, and (or) intermediate packaging with a different design (if any exist):

4.12.1. the application shall be prepared in the form according to Appendix 1 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.12.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition";

4.12.3. models of primary and secondary packaging (intermediate packaging - if any) of a medicinal product with a new labeling in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

4.13. when changing the number of doses in primary, intermediate or secondary packaging of a medicinal product or the amount of a pharmaceutical substance in a package of bulk product, or the amount of a pharmaceutical substance in a package of a pharmaceutical substance:

4.13.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.13.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition" (if the amendment affects the SmPC and the Basic Prescribing Information (package leaflet), registration of amendments into these documents in the form of a table "old edition and new edition" shall be essential);

4.13.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.13.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.13.5. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

4.13.6. a draft on amending the normative document on quality, if the amendments made affect this section of the master file, shall be in the form in accordance with Appendix 7.

In the event that the amendments in total affect more than half of the text of the normative document on quality or if there are more than three amendments, the normative document on quality in a new edition shall be submitted;

4.13.7. a copy of the Manufacturer's document confirming the quality of one batch of the medicinal product shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.26 of Clause 2 of these Instructions;

4.13.8. copies of the Manufacturer's documents containing the results of the stability study of the medicinal product and (or) bulk product (plan, report, tables with the research results), if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.18 and 2.30 of Clause 2 of these Instructions;

4.14. when changing the name of the medicinal product, the name of the dosage form, the method of indicating the dosage (for the medicinal product):

4.14.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.14.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition" (if the amendment affects the SmPC and the Basic Prescribing Information (package leaflet), registration of amendments into these documents in the form of a table "old edition and new edition" shall be essential);

4.14.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

4.14.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.14.5. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

4.14.6. other documents of the master file affecting the change in the name of the medicinal product, the name of the dosage form, the method of indicating the dosage (for the medicinal product), shall include, among other things, a draft amendments to the normative document on quality in the form in accordance with Appendix 7;

4.15. when reorganizing and (or) changing the name and (or) address without changing the actual location of the Manufacturer of the medicinal product, the Applicant and (or) the Holder of the Registration Certificate, including in the case of the presence of documents of the Manufacturer of the pharmaceutical substance in the master file for the medicinal product:

4.15.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.15.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition";

4.15.3. a notarized copy of a document confirming the reorganization and (or) change of the name and (or) address without changing the actual location of the Manufacturer of the medicinal product, the Applicant and (or) the Holder of the Registration Certificate. A document drawn up in a foreign language shall be accompanied by a translation into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). Documents shall be legalized and apostilled, unless otherwise provided by international treaties of the Republic of Belarus;

In case of the presence of the documents of the Manufacturer of a pharmaceutical substance in the master file for a medicinal product, a copy of the document confirming reorganization and (or) change of the name and (or) address without changing the actual location of the Manufacturer of the pharmaceutical substance shall be certified by the Holder of the Registration Certificate (Applicant). The document drawn up in a foreign language shall be accompanied by a translation into Belarusian or Russian, the accuracy of the translation shall be certified by the Holder of the Registration Certificate (Applicant);

4.15.4. documents of the master file affecting the reorganization and (or) change of the name and (or) address without changing the actual location of the Manufacturer of the medicinal product, the Applicant and (or) the Holder of the Registration Certificate, including in the case of the presence of documents of the Manufacturer of the pharmaceutical substance in the master file for the medicinal product shall include a draft amendments to the normative document on quality;

4.16. when changing the Manufacturer, country of manufacture (replacement or addition of a new production site for part or all of the manufacturing processes - for medicinal products, replacement or addition of a new production site for part of the manufacturing processes - for pharmaceutical substances) of a medicinal product, including if the pharmaceutical substance Manufacturer's documents are available in the master file for a medicinal product:

4.16.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.16.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition";

4.16.3. the original or a copy of the document confirming the registration of the medicinal product in the country of the Holder of the Registration Certificate (Manufacturer's country) (Registration Certificate or Certificate of Pharmaceutical Product in the format recommended by the World Health Organization) issued by the authorized body of the country of the Holder of the Registration Certificate (Manufacturer's country). The document shall contain information on the new manufacturer (new production site), the documents issued by the authorized body of the country of the Holder of the Registration Certificate (Manufacturer's country) shall be submitted in the original or as a notarized copy of the original with a translation into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). Documents shall be legalized and apostilled, unless otherwise provided by international treaties of the Republic of Belarus (for medicinal products of foreign manufacture);

4.16.4. omitted;

4.16.5. a copy of the license issued by the authorized body of the country of manufacture and granting the right to manufacture the medicinal product shall be notarized. The document shall be accompanied by a translation into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). Documents shall be legalized or apostilled, unless otherwise provided by international treaties of the Republic of Belarus (when making amendments to the master file for a medicinal product or pharmaceutical substance of foreign manufacture);

4.16.6. a copy of the document certifying the manufacture of a medicinal product under Good Manufacturing Practice conditions, issued by the authorized body of the country of manufacture of the medicinal product (for each participant in the manufacture of the medicinal product), shall be notarized. If there is no information in this document about the date of the recent inspection of the specified production, its validity period shall deem to be not more than 3 years from the date of its issue. Document shall be accompanied by a translation into Belarusian or Russian (the accuracy of the translation or the authenticity of the translator's signature shall be notarized). The document shall be legalized or apostilled, unless otherwise provided by international treaties of the Republic of Belarus (when making amendments to the master file for a medicinal product or pharmaceutical substance of foreign manufacture);

In the absence of a copy of a valid document certifying the manufacture of the medicinal product under Good Manufacturing Practice conditions issued by the authorized body of the country of manufacture of the medicinal product (for each participant in the manufacture of the medicinal product), a printout of a graphic screen image (screenshot) of the Internet page of the official website of the regulatory authority in the global computer network Internet containing information on the valid document certifying the manufacture of the medicinal product under Good Manufacturing Practice conditions issued by the authorized body of the country of manufacture of the medicinal product shall be submitted A printout of the graphic image of the screen (screenshot) of the web page of the official website of the regulatory authority of the country of manufacture of the medicinal product in the global computer network Internet shall be accompanied by a translation into Belarusian or Russian (the accuracy of the translation or authenticity of the translator's signature shall be notarized). The period of production of the printout shall not exceed 3 months from the date of submission of documents;

4.16.7. omitted;

4.16.8. omitted;

4.16.9. omitted;

4.16.10. copies of the documents of the new Manufacturer, including a description of the manufacturing process of a pharmaceutical substance, a concise manufacturing scheme, the size of the industrial batch, methods for confirming the structure, justification of impurities, a declaration or report on the validation of the manufacturing process (depending on which of the documents shall be submitted when registering medicinal products), CEP certificate (if any), if the changes made affect these sections of the master file, - for a pharmaceutical substance, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 3.4 and 3.5 of Clause 3 of these Instructions;

4.16.11. Manufacturer's document containing information on the composition of the medicinal product, indicating the amount of all ingredients, including all excipients per dosage unit (for dosed medicinal products) or unit of mass or volume (for non-dosed medicinal products) with reference to the documents on quality control of the pharmaceutical substances and excipients, shall comply with the requirements of Sub-clause 2.19 of Clause 2 of these Instructions;

4.16.12. copies of the Manufacturer's documents, including a description of the manufacturing process of the medicinal product, quality control of intermediate products, a concise manufacturing scheme, batch formula, the volume of an industrial batch, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.22 of Clause 2 of these Instructions;

4.16.13. copies of the reports on the validation of the manufacturing process of the medicinal product, if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.22 of Clause 2 of these Instructions;

4.16.14. a copy of the Manufacturer's document confirming the quality of one batch of the medicinal product shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.26 of Clause 2 of these Instructions;

4.16.15. copies of the Manufacturer's documents containing the results of the stability study of the medicinal product (plan, report, tables with the research results), if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.18 and 2.30 of Clause 2 of these Instructions;

4.16.16. copies of reports on the results of a comparative study of the bioavailability of a medicinal product manufactured at a new and previously approved production site, if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.33 and 2.34 of Clause 2 of these Instructions;

4.17. when changing the Applicant of the medicinal product and (or) the Holder of the Registration Certificate:

4.17.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

4.17.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition" (if the amendment affects the SmPC and the Basic Prescribing Information (package leaflet), registration of amendments into these documents in the form of a table "old edition and new edition" shall be essential);

4.17.3. the document (documents) confirming the right to be the Holder of the Registration Certificate or Applicant (if the Holder of the Registration Certificate does not manufacture the medicinal product), - contracts, license agreements confirming such right, other documents. Copies of contracts, license agreements shall be certified by one of the parties to these contracts, license agreements. Contracts, license agreements drawn up in a foreign language shall be accompanied by a translation into Belarusian or Russian, certified by one of the parties to these contracts, license agreements. Other documents (including an extract from the Trade Register of the country of the Holder of the Registration Certificate or the Applicant, a document confirming that the Applicant is a member of an association which also includes the Manufacturer of the medicinal product, the annual financial report of the Holder of the Registration Certificate or the Applicant) shall be submitted in the original or as notarized copies of other documents. Other documents drawn up in a foreign language shall be accompanied by a translation into Belarusian or Russian (the accuracy of the translation or authenticity of the translator's signature shall be notarized). Documents shall be legalized or apostilled, unless otherwise provided for by international treaties of the Republic of Belarus;

4.17.4. omitted;

4.17.5. omitted;

4.17.6. the draft SmPC shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions, if the amendments made affect this section of the master file;

4.17.7. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

4.17.8. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

4.17.9. other documents of the master file affecting the change of the Applicant of the medicinal product and (or) the Holder of the Registration Certificate shall include, among other things, the draft amendments to the normative document on quality in the form in accordance with Appendix 7.

5. Documents constituting the master file, for making amendments in the master file for a medicinal product of domestic manufacture shall comply with the following requirements:

5.1. when making amendments to the composition of the medicinal product (replacement or introduction of the additional Manufacturer of the pharmaceutical substance, introduction, exclusion or replacement of the excipients);

5.1.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

5.1.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition";

5.1.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

5.1.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

5.1.5. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

5.1.6. copies of Manufacturer's documents, including a description of the manufacturing process of a pharmaceutical substance, a concise manufacturing (synthesis) scheme, the information on the size of the industrial batch, methods of confirming the structure, justification of impurities, a declaration of manufacturing process validation or a CEP certificate (if any) and a report on validation of quality control methods, in case of replacement or introduction of the additional manufacturer of the pharmaceutical substance, that is a part of the medicinal product, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of the Sub-clause 2.15 of Clause 2 of these Instructions.

If there is no pharmacopoeial article (monograph) for a pharmaceutical substance in the State Pharmacopoeia of the Republic of Belarus, in the Pharmacopoeia of the Eurasian Economic Union, the European Pharmacopoeia, the British Pharmacopoeia or the US Pharmacopoeia, the following information shall be included in the document of the Manufacturer of the pharmaceutical substance:

on the concise synthesis scheme (manufacturing stages);

on the validation of the manufacturing process of the pharmaceutical substance (in the form of declaration);

on the methods for confirming the structure of the pharmaceutical substance;

on justifications of the impurities in the pharmaceutical substance;

on the confirmation of quality of one batch and results of incoming control of one batch of a pharmaceutical substance of the Manufacturer of the medicinal product.

In case of availability and upon submission of the CEP certificate, the document of the Manufacturer of the pharmaceutical substance shall include information confirming the quality of one batch and the results of the incoming control of one batch of the pharmaceutical substance of the Manufacturer of the medicinal product.

In case of confirmation in the document of the Manufacturer of the pharmaceutical substance of compliance of the quality of the pharmaceutical substance with the requirements of the State Pharmacopoeia of the Republic of Belarus, the Pharmacopoeia of the Eurasian Economic Union, the European Pharmacopoeia, the British Pharmacopoeia or the U.S. Pharmacopoeia, the following information shall be included in the document of the Manufacturer of the pharmaceutical substance:

on confirmation of the quality of one batch;

on the validation of the manufacturing process of the pharmaceutical substance (in the form of declaration);

on justifications of the impurities in the pharmaceutical substance;

on the confirmation of quality of one batch and results of incoming control of one batch of a pharmaceutical substance of the Manufacturer of the medicinal product.

5.1.7. copies of documents on quality control of the pharmaceutical substance and excipients, if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of the Sub-clauses 2.16 and 2.23 of Clause 2 of these Instructions;

5.1.8. copies of the Manufacturer's documents, containing the results of the stability study of the pharmaceutical substance (plan, report, tables with the research results), in the event of replacement or introduction of the additional manufacturer of the pharmaceutical substance, that is a part of the medicinal product, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.18 of Clause 2 of these Instructions;

5.1.9. the Manufacturer's document containing information on the composition of the medicinal product, indicating the amount of all ingredients, including all excipients per dosage unit (for dosed medicinal products) or unit of mass or volume (for non-dosed medicinal products) with reference to the documents on quality control of the pharmaceutical substances and excipients, shall comply with the requirements of Sub-clause 2.19 of Clause 2 of these Instructions;

5.1.10. copies of the Manufacturer's documents, including a description of the new manufacturing process of the medicinal product, quality control of intermediate products, a concise manufacturing scheme, batch formula, the volume of an industrial batch, the report on validation of the manufacturing process, if a change in composition entails a change in the production process, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.22 of Clause 2 of these Instructions;

5.1.11. the draft on amendments to the normative document on quality, if the amendments made affect this section of the master file, shall be prepared in the form according to Appendix 7.

In the event that the amendments in total affect more than half of the text of the normative document on quality or if there are more than three amendments, the normative document on quality in a new edition shall be submitted.

5.1.12. copies of reports on validation of medicinal product quality control methods, if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clause 2.25 of Clause 2 of these Instructions;

5.1.13. copies of the Manufacturer's document confirming the quality of one batch of a medicinal product and (or) excipients, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer);

5.1.14. copies of the Manufacturer's documents, containing the results of the stability study of the medicinal product (plan, report, tables with the research results), if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.18 and 2.30 of Clause 2 of these Instructions;

The results of stability studies of the medicinal product shall be presented for at least 3 months in long-term and accelerated studies for at least 2 batches, the volume of which is not less than the volume of the pilot-scale batch, and shall include information containing a commitment to continue long-term studies throughout the proposed shelf life and accelerated studies during 6 months and a commitment to study stability in long-term studies of the first industrial batch produced in accordance with the approved changes. The information shall include the information that the Ministry of Health will be informed immediately if any problems are detected related to the stability of the medicinal product.

5.1.15. copies of reports on the results of a comparative study of the bioavailability of a medicinal product with a new and previously registered composition shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.33 and 2.34 of Clause 2 of these Instructions.

In case of replacement of the manufacturer of the pharmaceutical substance, the copies of reports on the results of a comparative study of the bioavailability (in vivo studies) shall include the results of a comparative dissolution kinetics test;

5.2. in case of change of material, type of primary packaging, packaging components of the medicinal product (including in case of availability of documents of the manufacturer of the pharmaceutical substance in the master file for the medicinal product, which contains this pharmaceutical substance):

5.2.1. the application shall be prepared in the form according to Appendix 1 or Appendix 2 to the Regulations of the administrative procedure carried out in relation to the economic entities under sub-clause 9.4.3 "Making amendments to the master file";

5.2.2. the justification for the amendment made shall contain information on the nature and effectuality of the amendment being made. At the initiative of the Applicant, it shall be allowed to register the introduced amendment in the form of a table "old edition and new edition";

5.2.3. the draft SmPC, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.12 of Clause 2 of these Instructions;

5.2.4. the draft Basic Prescribing Information (package leaflet), if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.13 of Clause 2 of these Instructions;

5.2.5. models of primary and secondary packaging (intermediate packaging - if any) in Belarusian or Russian or in a foreign language with a sticker in Belarusian or Russian, if the amendments made affect this section of the master file, shall comply with the requirements of Sub-clause 2.14 of Clause 2 of these Instructions;

5.2.6. copies of documents on quality control of new packaging materials (new packaging components, new primary packaging components) and documents confirming that new primary packaging materials (new packaging components, new primary packaging components) of the medicinal product are suitable for packaging, contact with medicinal products, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer).

The documents shall include a description of the packaging or sealing system (primary packaging components), including a description of the materials from which each primary packaging component is made; specifications for primary packaging materials; copies of documents confirming that the primary packaging materials (primary packaging components) of the medicinal product are suitable for use for packaging of medicinal products. For medicinal products for oral and external use, the documents shall include information confirming the possibility to use the declared primary packaging materials for food products. For medicinal preparations for external use, the documents shall include information confirming the possibility of using the primary packaging materials for cosmetic products;

5.2.7. copies of documents confirming the quality of one series of new materials of primary packaging (new component parts of packaging, new components of primary packaging) shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer);

5.2.8. copies of the Manufacturer's documents containing the results of the stability study of the medicinal product in packaging made of new material or a new type of primary packaging (plan, report, tables with the research results), if the amendments made affect this section of the master file, shall be certified by the Holder of the Registration Certificate (Applicant, Manufacturer) and comply with the requirements of Sub-clauses 2.18 and 2.30 of Clause 2 of these Instructions.

The results of stability studies of the medicinal product shall be presented for at least 3 months in long-term and accelerated studies for at least 2 batches, the volume of which is not less than the volume of the pilot-scale batch, and shall include information containing a commitment

to continue long-term studies throughout the proposed shelf life and accelerated studies during 6 months and a commitment to study stability in long-term studies of the first industrial batch produced in accordance with the approved changes. The information shall include the information that the Ministry of Health will be informed immediately if any problems are detected related to the stability of the medicinal product.

Appendix 1
omitted

Appendix 2
to the Instructions on the
requirements for the documents
that make up
the master file

Form

STAMP OF RECORD AGREEMENT

NORMATIVE DOCUMENT ON QUALITY

Name of the medicinal product, dosage form, dosage:

_____

(international non-proprietary name (in its absence - common (grouping) name, Latin name of the producing plant for herbal medicinal products, which are packaged medicinal plant raw materials *)

Holder of Registration Certificate (Applicant): _____

(name and country)

Manufacturer carrying out the manufacture of the finished dosage form:

_____

(name and country)

Manufacturer carrying out the packing and (or) packaging:

_____

(name and country)

Manufacturer performing quality control:

_____

(name and country)

Manufacturer issuing a release permit:

_____

(name and country)

_____

* For a herbal medicinal product (crushed or whole packaged raw materials, briquettes, mixtures, filter bags, etc.), the name of the medicinal plant raw material is indicated in Belarusian or Russian and in Latin.

In the name of medicinal plant raw materials in the first place indicate the name of the producing plant in the genitive case, in the second - the raw part of the plant, in the nominative plural (except for "bark", "grass"), and as an additional element, the sign of its grinding, packaging.

Example: Linden flowers, whole (or crushed), 50 g.

Linden flowers, coarse powder 1.2 g in filter bags No. 20.

In the name of the mixtures, in the first place, indicate the trade name in the nominative case, then indicate the dosage form (mixture) and packaging (package weight or number of doses in a package).

Example: Gastric mixture No. 3, mixture 50 g.

Appendix 3
to the Instructions on the
requirements for the documents
that make up
the master file

LIST
of sections of the report on preclinical (nonclinical) studies of the medicinal product

1. Pharmacology
1.1. Primary pharmacodynamics
1.2. Secondary pharmacodynamics
1.3. Pharmacological safety
1.4. Pharmacodynamic drug interactions
2. Pharmacokinetics
2.1. Analytical methodologies and validation reports
2.2. Absorption
2.3. Distribution
2.4. Metabolism
2.5. Excretion (elimination)
2.6. Pharmacokinetic drug interactions
2.7. Other pharmacokinetic studies
3. Toxicology
3.1. Single dose toxicity
3.2. Repeated dose toxicity
3.3. Genetic Toxicology
3.4. Carcinogenicity
3.5. Reproductive and developmental toxicity: fertility and early embryonic development, embryo-fetal development, prenatal and postnatal development, studies on immature offspring with follow-up
3.6. Local tolerance
3.7. Other toxicological studies: antigenicity, immunotoxicity, mechanistic studies, drug dependence, metabolites, impurities and other studies
4. Copies of used literary sources.

Appendix 4
omitted

Appendix 5
to the Instructions on the
requirements for the documents
that make up
the master file (attached)

Form

STAMP OF RECORD AGREEMENT

NORMATIVE DOCUMENT ON QUALITY

The name of the pharmaceutical substance*:

_____
(international non-proprietary name (if any))

Holder of Registration Certificate (Applicant):

_____
(name and country)

Manufacturer of pharmaceutical substance:

_____
(name and country)

* If a pharmaceutical substance is sterile, when indicating its name, it is additionally indicated: “sterile”.

Appendix 6
omitted

Appendix 7
to the Instructions on the
requirements for the documents
that make up
the master file (attached)

Form

STAMP OF RECORD AGREEMENT

AMENDMENTS TO THE NORMATIVE DOCUMENT ON QUALITY

AMENDMENT NO. _____
(next reference number)

_____
(name of the medicinal product, dosage form, dosage
or name of the pharmaceutical substance)

Old edition	New edition

_____
(page number)