(Unofficial translation)

RESOLUTION OF THE MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS
No. 93 dated November 2, 2020

On the preliminary technical activities preceding the state registration of medicinal products

Amendments and additions:

Resolution of the Ministry of Health of the Republic of Belarus dated December 21, 2021 No. 126 (registered in the National Register – No. 8/37519 dated January 10, 2022);

Resolution of the Ministry of Health of the Republic of Belarus dated April 22, 2022 No. 37 (registered in the National Register – No. 8/38138 dated May 25, 2022);

Resolution of the Ministry of Health of the Republic of Belarus dated August 22, 2022 No. 88 (registered in the National Register – No. 8/38673 of September 6, 2022);

Resolution of the Ministry of Health of the Republic of Belarus dated October 6, 2023 No. 163 (registered in the National Register – No. 8/40832 dated December 19, 2023).

Based on the paragraph of the second subclause 8.14^1 of clause 8 and subclause 9.1 of clause 9 of the Regulation on the Ministry of Health of the Republic of Belarus approved by Resolution of the Council of Ministers of the Republic of Belarus dated October 28, 2011 No. 1446, part two of clause 3 and clause 4 of the Regulation on the procedure and terms for the state registration (state registration endorsement) of medicinal products approved by Resolution of the Council of Ministers of the Republic of Belarus dated April 1, 2015 No. 254, the Ministry of Health of the Republic of Belarus SHALL DECIDE TO:

1. Approve the Instructions on the procedure for carrying out preliminary technical activities preceding the state registration of medicinal products (see Appendix).

2. Eliminate paragraph two of clause 1 of resolution of the Ministry of Health of the Republic of Belarus dated April 23, 2015 No. 55 “On the preliminary technical activities preceding the state registration of medical devices”.

3. This resolution becomes effective on November 20, 2020.

Deputy Minister **B. N. Androsyuk**

APPROVED

Resolution
Ministry of Health
Republic of Belarus
2.11.2020 No. 93

INSTRUCTION

On the procedure for carrying out preliminary technical activities preceding the state registration of medicinal products

1. This Instruction shall determine the procedure for the Republican Unitary Enterprise "Center for Examination and Tests in Health Service" (hereinafter the Center, unless otherwise indicated) to carry out (hereinafter the preliminary technical activities, unless otherwise indicated) in respect to examinations, quality control method validation and quality control using these methods (hereinafter validation and quality control), other investigations to validate compliance of the medicinal product with the safety, efficacy and quality requirements. The preliminary activities are foregoing to the state registration (state registration endorsement) of medicinal products, conditional state registration (conditional state registration endorsement) of medicinal products and making amendments to the registration dossier.

This Instruction shall not be applicable to:

Examinations to be conducted during registration (registration endorsement) and other procedures related to the registration of medicinal products within the Eurasian Economic Union;

Preliminary technical activities preceding the state registration of medicinal products using the simplified procedure as set forth in the Regulation on the simplified procedure for state registration of medicinal products approved by Resolution of the Council of Ministers of the Republic of Belarus dated April 1, 2020 No. 191;

The preliminary technical activities preceding the state registration of strategically important medicinal products as set forth in the Regulation on the procedure and terms for the state registration of strategically important medicinal products approved by Resolution of the Council of Ministers of the Republic of Belarus dated October 8, 2021 No. 570.

2. This Instruction uses terms and their definitions in the meanings established by Law of the Republic of Belarus dated July 20, 2006 No. 161-Z "On the Circulation of Medicines".

3. The preliminary activities shall be carried out under agreements for specific types of activities concluded between the Center and the applicant. The total period for preliminary activities should not exceed 180 calendar days. This period may be extended to 360 calendar days upon mutual agreement of the parties.

For the preliminary activities to be implemented, the applicant shall submit the documents of the registration dossier to the Center as per the list shown in Appendix 1 to the Regulation on the procedure and terms for state registration (state registration endorsement) of medicinal products (hereinafter the documents).

4. The preliminary activities include:

4.1. Primary expert evaluation of documents (hereinafter the primary expert evaluation) providing for:

Checking for completeness and accuracy of the documents;

Compliance assessment of the trade name of the medicinal product with the criteria established by Decree of the Ministry of Health of the Republic of Belarus dated September 24, 2020 No. 78 "On the Criteria for Trade Names of Medicinal Products".

The primary expert evaluation shall be made by a specialist of the Center under the agreement concluded between the Center and the applicant within a period not exceeding 5 working days from the date of receipt of these documents.

An expert opinion shall be prepared based on the results of the primary expert evaluation with conclusions including:

Compliance (non-compliance) of the submitted documents with the statutory requirements. If no document (certificate) to validate compliance of the commercial manufacturing of medicinal products with the principles of Good Manufacturing Practice issued by the Ministry of Health, or document (certificate) to validate compliance of the commercial manufacturing of medicinal products with the principles of Good Manufacturing Practice of the Eurasian Economic Union issued by a competent authority of a member state of the Eurasian Economic Union (hereinafter referred to as the GMP certificate) are available, the expert opinion shall indicate the need for an inspection (pharmaceutical inspection) of the commercial manufacturing of medicinal products to obtain a GMP certificate within the period established for the preliminary activities to validate;

Compliance (non-compliance) of the trade name of the medicinal product with the stated criteria.

The expert opinion specified in part three of this subclause shall be sent to the applicant in writing and/or electronically within 5 working days from the date of signing. If no GMP certificate is available, the above expert opinion shall be also sent to the Ministry of Health by the Center within the same period.

If the expert opinion specified in part three of this subclause provides conclusions on non-compliance of the submitted documents with the statutory requirements and/or non-compliance of the trade name of the medicinal product with the established criteria, the documents shall be returned to the applicant and the preliminary activities shall be terminated.

In case of positive primary expert evaluation, the documents shall be sent for specialized examination;

4.2. The specialized examination, which is an assessment of documents to validate compliance of the medicinal product with the safety, efficacy and quality requirements considering their chemical, pharmaceutical and clinical pharmacological characteristics (hereinafter referred to as the specialized examination).

A specialized examination shall be performed under a separate agreement concluded between the Center and the applicant within a period not exceeding 30 working days from the date of receipt of monetary funds to the Center’s current account.

The specialized examination shall be conducted by:

Experts who are specialists of the Center (hereinafter the Center specialists) and members of the expert groups of the Commission on medicinal products of the Ministry of Health (hereinafter the Commission);

Experts who are not specialists of the Center and members of the expert groups of the commission for cases specified in part four of this subparagraph;

Experts appointed by the Ministry of Health and qualified in the scope of clinical use of the medicinal product provided that they are not members of the expert groups of the commission for cases specified in part five of this subparagraph.

A specialized examination shall be conducted by the experts specified in paragraph three of part three of this subclause in the cases including:

State registration of a medicinal product having a new active substance not previously registered in the Republic of Belarus;

State registration (state registration endorsement), making amendments to the registration dossier of biotechnological, immunological medicinal products;

Conditional state registration (conditional state registration endorsement) of a medicinal product, making amendments to the registration dossier for a medicinal product previously registered in accordance with the procedure and terms for conditional state registration;

Addition of a new indication and/or new mode of administration (injection) to the Summary product characteristics, Instructions for medical use (insert leaflet) for an originator pharmaceutical product or, if not available, for a generic medicinal product first declared;

On the recommendation of the expert(s) of the Center with the justification submitted in the expert opinion as per part six of this subparagraph;

The applicant's disagreement with the comments of the Center's expert(s) on their written appeal;

The commission's decision.

A specialized examination shall be conducted by the experts specified in paragraph four of part three of this subclause in the cases including:

Conditional state registration (conditional state registration endorsement) of a medicinal product;

Amendments to the registration dossier for a medicinal product previously registered in accordance with the procedure and terms for conditional state registration.

Each expert shall provide their expert opinion based on the results of the specialized examination.

In case of any comments submitted in the expert opinions as outlined in part six of this subclause, the Center shall send them to the applicant (with no indication of the experts) in writing and/or electronically within 5 working days from the date of their signing.

When addressing the comments, the applicant shall submit the documents and/or materials to the Center confirming elimination of the faults contained in the comments in writing and/or electronically within a period not exceeding 60 calendar days from the date of their receipt. The specified period shall not be counted in the term required for the implementation of the preliminary activities.

The Center reviews the documents and/or materials submitted by the applicant within a period not exceeding 15 working days from the date of their submission. Subsequent comments are allowed only if further matters arise regarding the documents and/or materials submitted by the applicant in response to preceding comments.

Should an expert(s) identify the information that is undermining to reliability of the information of the documents provided by the applicant on the clinical studies (trials) of the medicinal product or the Marketing Authorization holder's pharmacovigilance management and functioning, the expert opinion as outlined in part six of this subclause shall indicate the need for compliance inspection (pharmaceutical inspection) in respect to:

Conducted clinical studies (trials) of the medicinal product with the requirements of the Good Clinical Practice regulations of the Eurasian Economic Union;

The Marketing Authorization holder's pharmacovigilance management and functioning as per the requirements of Good Pharmacovigilance Practice rules of the Eurasian Economic Union.

The expert opinion prepared as shown in part ten of this subparagraph shall be sent to the applicant by the Center and the Ministry of Health within 5 working days from the date of its signing.

The inspection (pharmaceutical inspection) outlined in paragraphs two and three of part ten of this subclause shall be conducted within the period required for the implementation of the preliminary activities;

4.3. Validation and quality control which are to be conducted by the Center's pharmacopoeial and pharmaceutical analytical laboratory (hereinafter the Center's laboratory) under a separate agreement concluded between the Center and the applicant within a period not exceeding 90 calendar days from the date of receipt of monetary funds to the Center's current account. For quality parameters involving multi-level testing and result assessment, in case of first-level ambiguous or negative results requiring subsequent level testing, validation and quality control testing period can be extended to 120 calendar days under a supplementary agreement to the agreement previously made.

Validation and quality control shall be ensured for medicinal products newly submitted for the state registration, and when making changes to the registration dossier with respect to quality changes made to the regulatory document.

Validation and quality control shall not be provided for:

Narcotic drugs and psychotropic substances;

Radiopharmaceuticals;

Orphan (rare-disease) drugs;

Medicinal products submitted for conditional state registration;

Pharmaceutical substances for which the quality control methods and quality parameters are consistent with the quality control methods and quality parameters set out in specific pharmacopoeial monographs of the State Pharmacopoeia of the Republic of Belarus, or European Pharmacopoeia if no such monographs are available in the State Pharmacopoeia of the Republic of Belarus.

Samples of medicinal products and reference standards as well as microbial test strains, cell cultures, diagnostic test kits, chromatographic columns, specific supplies and reagents of the pharmaceutical manufacturer required for validation and quality control shall be provided by the applicant to the Center. Reference standards, specific supplies and chromatographic columns remaining after testing shall be returned to the applicant on request.

If the Center lacks technical capabilities, validation and quality control shall be carried out by testing laboratories accredited in the National Accreditation System of the Republic of Belarus for pharmaceutical testing (hereinafter the testing laboratories) of the Republican Research and Practical Center for Epidemiology and Microbiology and the Republican Research and Practical Center for Transfusiology and Medical Biotechnology under agreements concluded with the Center if their available technologies allow for specific types of testing.

If the Center and the testing laboratories lack technologies sufficient for validation and quality control and if the applicant is not able to provide samples of the medicinal product, reference standards, microbial test strains, cell cultures, diagnostic test kits, chromatographic columns, specific supplies and reagents of the manufacturer of the medicinal product, validation and quality control shall be carried out at the address of the manufacturer of the medicinal product involved in quality control assisted by specialists of the Center's laboratory and testing laboratories (if required). If there is no way that the specialists of the Center's laboratory and testing laboratories can be involved in the validation and quality control at the address of the manufacturer of the medicinal product due to external factors beyond the Center's and testing laboratories control, these tests might be conducted

based on the the submitted documentation and manufacturer's materials using means of remote interaction including through audio and video communication and video recording.

If documented by the applicant that the cost of drug samples required for validation and quality control exceeds 1000 conventional units which is equivalent to 1000 US dollars at the rate of the National Bank of the Republic of Belarus on the date of document submission by the applicant for primary expert evaluation, validation and quality control shall be carried out for individual parameters of the quality regulatory document used to validate identification, assay of active ingredients and related impurities.

Following the validation and quality control, the Center and/or testing laboratories shall prepare a validation report(s) and a test protocol(s) for the medicinal product and send it to the applicant in writing and/or electronically within a period not exceeding 5 working days from the date of their signing. Based on the results of validation and quality control of the medicinal product using remote interaction means or that conducted at the address of the manufacturer involved in quality control, the applicant shall prepare the test results to be signed (certified) by the manufacturer responsible for quality control of the medicinal product. The center and testing laboratories (if necessary) shall prepare a validation report to be sent to the applicant in writing and/or electronically within a period not exceeding 5 working days from the date of signing. If there are comments in the validation report(s), the applicant shall address them within a period not exceeding 60 calendar days from the date the applicant receives the drug test protocol(s) and/or the validation report(s). This period may be extended for up to 90 calendar days based on a reasonable written request from the applicant. The specified period shall not be counted in the term required for the implementation of the preliminary activities.

The applicant's elimination of the faults noted in the comments of the validation report requiring no re-validation shall be confirmed by the Center's laboratory and documented in the validation report within a period not exceeding 15 calendar days from the submission date of documents and materials confirming the elimination of the faults noted in the comments.

To confirm that the applicant has addressed the comments requiring re-validation, the Center's laboratory shall ensure re-validation and quality control. In this case, the validation and quality control period can be extended to 180 calendar days from the submission date of documents and materials required to confirm the elimination of the faults noted in the comments. The results shall be documented in a validation report and a test protocol for the medicinal product.

Subsequent comments shall be forwarded to the applicant only if further questions arise regarding the information (materials) submitted by them in response to the preceding comments.

5. Based on the results of the preliminary activities, the Center shall prepare a statement of compliance (non-compliance) for the medicinal product with the safety, efficacy and quality requirements (hereinafter the statement) in the form as shown in Appendix.

6. The statement shall be prepared in two copies, signed by a competent authority and sealed by the Center. One copy of the statement shall be sent to the applicant within 5 working days from the date of its signing while the second copy shall be stored in the Center.

The statement's validity period is 6 months from the issue date.

7. At the applicant's instigation, the preliminary activities may be terminated and in this case, the Center shall issue no statement.

Appendix
To the Instructions on the
Procedure of Preliminary
Technical Activities Preceding the
State Registration of Medicinal
Products

Form

REPUBLICAN UNITARY ENTERPRISE
"CENTER FOR EXAMINATION AND TESTING IN HEALTHCARE"

STATEMENT
On compliance (non-compliance) of the medicinal product with the safety, efficacy and quality requirements

___ _____ 20 Minsk

This statement has been prepared based on the results obtained from preliminary technical activities preceding the state registration of medicinal products, endorsement of state registration of medicinal products, conditional state registration (conditional state registration endorsement) of medicinal products, making amendments to the registration dossier (underline as appropriate)

_____
(Trade name of the medicinal product/pharmaceutical substance,

_____
Dosage form (to be specified for the medicinal product), Marketing Authorization holder's and manufacturer(s') name and country

_____
(Trade name of the medicinal product/pharmaceutical substance

_____
(Complies (fails to comply) with the safety, efficacy and quality

_____
requirements)

_____

This statement is valid for 6 months from the issue date.

_____	_____	_____
(Competent authority position)	(Signature)	(Initials (name initial), surname)

L.S.