On approval of the Rules of temporary state registration of vaccines against Covid-19

Unofficial translation

Resolution of the Government of the Republic of Kazakhstan dated December 15, 2020 No. 850.

Unofficial translation

Footnote. Title as amended by the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

In accordance with subparagraph 9) of Article 6 of the Code of the Republic of Kazakhstan "On health of the people and the healthcare system" and paragraph 1 of the resolution of the President of the Republic of Kazakhstan dated March 16, 2020 No. 286 "On measures to ensure socio-economic stability" The Government of the Republic of Kazakhstan **hereby RESOLVED as follows**:

Footnote. The preamble - in the wording of the resolution of the Government of the Republic of Kazakhstan of 17.08.2022 No. 566 (shall enter into force from the day of its first official publication).

1. To approve the attached Rules of temporary state registration of vaccines against Covid -19.

Footnote. Paragraph 1 as amended by the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

2. This resolution shall come into force from the date of its first official publication.

Prime Minister
of the Republic of Kazakhstan *A. Mamin*

Approved
by the Resolution
of the Government of the
Republic of Kazakhstan
dated December 15, 2020 No. 850

The Rules of temporary state registration of vaccines against Covid-19

Footnote. The title as amended by the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

Chapter 1. General Provisions

1. These Rules for the temporary state registration of vaccines against coronavirus COVID-19 (hereinafter referred to as the Rules) have been developed in accordance with subparagraph 9) of Article 6 of the Code of the Republic of Kazakhstan "On health of the people and the healthcare system" (hereinafter referred to as the Code), paragraph 1 of the

resolution of the President of the Republic of Kazakhstan dated March 16, 2020 No. 286 "On measures to ensure socio-economic stability" and determine the procedure for conducting temporary state registration of vaccines against coronavirus COVID-19 for the production of an experimental and industrial batch (hereinafter referred to as the vaccine).

Footnote. Paragraph 1 - in the wording of the resolution of the Government of the Republic of Kazakhstan dated 17.08.2022 No. 566 (shall enter into force from the day of its first official publication).

2. In these Rules, the following basic concepts are used:

1) a state body in the field of circulation of pharmaceuticals and medical devices - a state body that exercises leadership in the field of circulation of pharmaceuticals and medical devices, control over the circulation of pharmaceuticals and medical devices (hereinafter referred to as the state body);

2) a state expert organization in the field of circulation of pharmaceuticals and medical devices - a state monopoly entity carrying out production and economic activities in the field of public health to ensure the safety, efficiency and quality of pharmaceuticals and medical devices (hereinafter referred to as the state expert organization);

3) vaccines - medicinal products for specific prophylaxis of infectious diseases, providing a preventive effect through the immune system;

4) expert commission – a collegial body, created in a state expert organization, for consideration of documents and making a conclusion on the safety, quality and efficacy of vaccines;

5) an applicant – an individual or legal entity entitled to apply for temporary state registration of coronavirus COVID-19 vaccines produced in the Republic of Kazakhstan;

6) central bioethics commission – an independent expert body under the authorized body in the field of health, conducting a bioethical examination of documents related to the conduct of medical research, at the stage of their planning, during their implementation and after completion in order to ensure the safety and protection of the rights of participants in medical research;

7) amendments to the registration dossier of the vaccine - the procedure carried out on the basis of an examination of the changes made to the registration dossier of the vaccine during the validity period of the temporary registration certificate.

Footnote. Paragraph 2 as amended by the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

Chapter 2. Procedure for temporary state registration of coronavirus COVID-19-vaccines produced in the Republic of Kazakhstan

3. For the temporary state registration of vaccines, the applicant shall submit to the state expert organization an application and a list of documents according to the forms in accordance with Annexes 1 and 2 to these Rules.

Before submitting an application, the applicant, on his own initiative, receives scientific and pre-registration consultations with the state body and (or) the state expert organization on issues related to the temporary state registration of vaccines against coronavirus COVID-19.

Footnote. Paragraph 3 - in the wording of the resolution of the Government of the Republic of Kazakhstan dated 17.08.2022 No. 566 (shall enter into force from the day of its first official publication).

4. To consider the documents submitted by the applicant, the state expert organization, within 1 (one) business day from the date of registration of the application, shall form an expert commission, consisting of:

1) specialists and experts of the state expert organization;

2) representatives of the central bioethics commission;

3) representatives, specialists and experts of medical organizations;

4) representatives, specialists and experts of specialized organizations operating in the field of medicine, biology, microbiology, immunology and epidemiology.

5. The structure of the expert commission is approved by order of the head of the state expert organization.

The chairman of the expert commission is a person not lower than the deputy head of the state expert organization. The total number of members of the expert commission is odd.

The meeting of the expert commission is considered competent if at least two-thirds of the total number of members of the expert commission is present, a video or audio recording of meetings is made. The results of the meeting of the expert commission are drawn up by the relevant protocol, which is signed by all members of the expert commission.

The decisions of the expert commission are made by voting by a majority vote of the number of members of the expert commission present at the meeting.

With the equality of votes, the chairman's voice is decisive.

A member of the expert commission is not authorized to transfer the right to vote to another person, including another member of the expert commission.

A member of the expert commission, who did not agree with the opinion of the majority, is authorized within a day from the date of end of the meeting to submit in writing his special opinion for introduction to the protocol.

Any interference in the activities of the expert commission is not allowed.

It is not allowed to include in the expert commission, as well as the involvement of persons who are representatives of the applicant, as well as persons who directly or indirectly participated in the preparation and (or) development of the vaccine, for a different form of participation in the work of the expert commission.

Footnote. Paragraph 5 as amended by the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

6. The expert commission within 10 (ten) working days shall assess the completeness of the submitted documents and their consideration in compliance with the principles of independence, objectivity.

If there are any questions or comments to the submitted documents, the state expert organization shall send the applicant, within a period of not more than 1 (one) business day from the date of registration of the application, an official request (in any form) about the need to provide additional clarification and (or) eliminate the identified comments in in full within a period not exceeding 3 (three) working days.

In cases where the applicant submits an incomplete package of documents, as well as the failure to eliminate the comments of the expert commission within the time limits provided for by this paragraph, the expert commission shall issue a negative opinion.

7. The results of the meeting of the expert commission shall be drawn up by the appropriate protocol and signed by all members of the expert commission.

8. Based on the results of consideration and discussion, the expert commission, within 1 (one) working day, shall form a conclusion on the safety, quality and effectiveness of the vaccine in the form according to Appendix 3 to these Rules.

9. The state body, on the basis of the conclusion on the security, quality and efficiency of the vaccine, submitted by the expert commission, within 1 (one) working day, decides on temporary state registration of the vaccine for a period of 18 (eighteen) months or refuses the temporary state registration of the vaccine.

Footnote. Paragraph 9 as amended by the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

10. In case of a positive decision, the state body within 1 (one) working day shall issue a temporary registration certificate to the applicant in the form according to Appendix 4 to these Rules.

11. In the event of a negative decision, the state body within 1 (one) working day shall notify the applicant in writing (arbitrary) of the refusal of the temporary state registration of the vaccine, indicating the reasons for the refusal.

The grounds for the refusal shall be the negative conclusion of the expert commission.

12. Medical use on a voluntary basis of vaccines that have received a temporary registration certificate before the applicant submits to the state body reports of phases I-II of clinical trials and an interim report of phase III of studies conducted with the inclusion of at least 50 (fifty)% of research subjects provided for by the protocol of the clinical trial shall not be allowed , except for medical use conducted within the framework of clinical trials.

13. In the course of medical use of vaccines in the framework of an ongoing clinical trial or medical use of vaccines on a voluntary basis, who have received a temporary marketing authorization based on the results of phases I-II clinical trials and an interim report of phase

III studies conducted with the inclusion of at least fifty (50)% of research subjects stipulated by the clinical trial protocol, the state body shall make a decision to suspend or cancel the validity of the temporary marketing authorization in cases:

1) revealing and (or) obtaining data on the occurrence of adverse vaccine reactions;

2) revealing and (or) obtaining data on the unfavorable benefit-risk ratio of the vaccine;

3) the presence of a court decision that has entered into force on the violation of the exclusive rights of third parties to an invention or utility model.

During the period of validity of the temporary registration certificate, the applicant shall submit full reports of phases I - II of clinical trials and an interim report of phase III of studies conducted with the inclusion of at least 50 (fifty)% of the research subjects provided for by the protocol of the clinical trial.

14. Upon the expiration of the temporary registration certificate, the applicant shall submit to the expert commission the results of clinical studies on the safety, quality and efficacy of the vaccine obtained during the validity period of the temporary registration certificate.

15. The expert commission within 7 (seven) working days shall consider the information submitted by the applicant.

In case of positive results of clinical trials of a vaccine on its medical use, the applicant, who owns a temporary registration certificate, shall undergo the examination procedure and state registration of medicines and medical devices in accordance with the requirements of Article 23 of the Code.

Chapter 3. Procedure for issuance of a temporary registration certificate to vaccines against Covid-19, produced outside the Republic of Kazakhstan

Footnote. The rules are supplemented by Chapter 3 in accordance with the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

16. The state body, taking into account the epidemiological situation in the Republic of Kazakhstan, sends a request to the state expert organization on the need to verify the availability of registration of the vaccine in the country of the manufacturer and the compliance of the manufacturer of the vaccine with the requirements of the GMP.

The state expert organization within 3 (three) working days from the date of registration of a request from a state body checks and analyzes the available information from open official, Internet resources and other sources about:

1) registration of the vaccine in the country of the applicant-manufacturer;

2) compliance of the manufacturer of the vaccine with the requirements of GMP.

According to the results of the work, the expert organization sends the opinion of the state expert organization to the state body on the presence/absence of registration of the vaccine in the country of the manufacturer and the compliance/non-compliance of the production site with the requirements of the GMP.

17. Temporary registration certificate of vaccines against Covid-19, produced outside the Republic of Kazakhstan, is issued provided that the relevant decision of the interdepartmental commission for prevention and non-spread of the coronavirus infection in the Republic of Kazakhstan is available (order of the Prime Minister of the Republic of Kazakhstan dated January 27, 2020 No. 10-p) and on the basis of the opinion of the state expert organization on the availability of registration of the vaccine in the country of the manufacturer and the compliance of the production site with the requirements of GMP.

18. A temporary registration certificate is issued for up to 8 (eight) months.

Chapter 4. Procedure for amending the registration dossier of vaccines with a temporary registration certificate

Footnote. The rules are supplemented by Chapter 4 in accordance with the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

19. During the validity period of temporary registration certificate, the applicant for amendments to the registration dossier submits to the state expert organization:

1) an application for amendments to the registration dossier of the vaccine in the form in accordance with Appendix 5 to these Rules;

2) documents in accordance with the list of changes made to the registration dossier of the vaccine, in accordance with Appendix 6 to these Rules.

The state expert organization registers the application on the day of receipt and submits the documents received to the expert commission for consideration.

20. The expert commission within 10 (ten) working days from the date of submission of documents for consideration assesses the completeness of the submitted documents and their consideration in compliance with the principles of independence, objectivity.

If there are questions or comments on the documents submitted, the expert commission sends to the applicant within no more than 1 (one) working day from the date of submission of documents for consideration, the official request (in any form) on the need to provide additional clarification and (or) eliminate the revealed comments in full at a time not exceeding 3 (three) working days.

21. According to the results of the consideration and discussion of the application and documents, the expert commission within 1 (one) working day forms a conclusion on amendments to the registration dossier of the vaccine in the form in accordance with Appendix 7 to these Rules.

In cases when the applicant submits an incomplete package of documents, as well as not full elimination of the comments revealed by the expert commission, a negative conclusion is issued by the expert commission.

In cases where the applicant submits an application and a package of documents that meet the requirements of these Rules, the expert commission issues a positive conclusion.

22. The state body on the basis of the conclusion submitted by the expert commission within 1 (one) working day decides to amend the registration dossier, with the issuance of an updated temporary registration certificate in accordance with Appendix 4 to these Rules, or refuses to amend the registration dossier of the vaccine.

Appendix 1
to the Rules of temporary state
registration of vaccines against
Covid-19

Footnote. The text in the upper right corner of Appendix 1 as amended by the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

Form

Application for temporary state registration of a vaccine

1.	Type of procedure	Temporary registration ☐	
2.	Trade name	in Kazakh	
		in Russian	
		in English	
3.	International Non-proprietary Name	in Kazakh	
		in Russian	
		in English	
4.	Pharmaceutical form	in Kazakh	
		in Russian	
5.	Dosage (concentration) (filled if available, volume filled in the package)	The concentration is indicated for liquid, soft and gaseous dosage forms.	
6.	Anatomical-therapeutic-chemical classification	Code	
		Name in Kazakh	
		Name in Russian	
7.	Type of medicinal product (to be filled in for the corresponding medicinal product, only one type of medicinal product is selected)		
1)	☐ Originator pharmaceutical product		
	☐ Single-component	☐ Multi-component	
	☐ Biological pharmaceutical product	☐ Immunobiological pharmaceutical product	
	☐ New active pharmaceutical substance	☐ Bulk product	

2)	☐ Active pharmaceutical substance, which is not produced under GMP conditions								
8.	Form of dispensing in the country of the applicant	Prescribed by a doctor; Without doctor's prescription.							
9.	Methods of administration								
10.	Information about devices for administration								
11.	Packing (complete the list of values)								
№	Type (primary or secondary)	Name	Size (if available)	Volume (if available)	Number of units in a package	Brief description			
1)	Primary								
2)	Intermediate (if available)								
3)	Secondary								
4)	Secondary Packaging Barcode (GTIN) (if available)	Indicate barcode for each dosage (concentration)							
12.	Complete qualitative and quantitative composition (complete the list of values)								
Item No.	Type of substance (active or auxiliary)	Name	Quantity per unit of a pharmaceutical form	Normative document regulating quality, or pharmacopoeia indicating the year of publication	Manufacturer, country and address of the production site (for active substances)	Controlled by the International Narcotics Control Board (marked if available)	The presence of toxic substances (marked if available)	Wild or cultivated (for medicinal plant materials) and place of growth	Marker of human or animal origin (marked if available)
1)	Active					II tab.III tab.IV tab.	1 list 2 list		
2)	Auxiliary								
13.	Name of active pharmaceutical substance								
		suggested shelf life							

14.	Shelf life of a pharmaceutical product	suggested period of use (after the first opening of the container)						
		suggested period of use (after dissolution or dilution)						
15.	Transportation conditions							
16.	Storage conditions	Suggested storage conditions						
		Suggested storage conditions after the first opening of a package						
17.	Title of protection for the invention or a utility model, trade mark (if available)							
	Name of the title of protection	No. of the title of protection			Date of issue	Time limit for issuance		
18.	Production	1) completely in the given production; 2) partially in this production; 3) completely in another production.						
19.	Manufacturer (s) of the medicinal product and production site (s) (including the production areas of any component (including the solvent of the dosage form) that is part of the medicinal product)							
Item No.	Type of manufacturer	Name, country (in Kazakh, Russian, English)	No., date and validity period of the authorization document	Legal address	Current address	Telephone, fax, e-mail	Surname, name, patronymic (if available), position of the head	Surname, name, patronymic (if available), position of the contact person
1)	Manufacturer							
2)	Packing company							
3)	primary							
4)	secondary							
5)	Manufacturer exercising quality control							
6)	Manufacturer responsible for							

	batches release							
7)	License holder		Data on the production license issued by the authorized body of the manufacturer's country					
8)	Registration certificate holder							
9)	Applicant or representative office		Data according to the power of attorney					
10)	Authorized person for pharmacovigilance in the Republic of Kazakhstan							
20.	Laboratory of the country of origin for quality control of blood products and vaccines, responsible for quality control (batch release)							
1)	name of the laboratory							
2)	address of the place of business							
3)	Country							
4)	Telephone/fax							
5)	e-mail							
22.	Data on the Agreement for the examination of medicines							
1)	Agreement No.							
2)	Date of conclusion							
3)	Validity period							
23.	Entity that performs payment for the examination							
1)	Name							
2)	Country							
3)	Legal address							

4)	Current address	
5)	Surname, name, patronymic (if available), position of the head	
6)	Telephone	
7)	Fax	
8)	e-mail	
9)	Business identification number	
10)	Individual identification number	
11)	Bank	
12)	Current account	
13)	Foreign currency account	
14)	Code	
15)	Bank identification code	
Applicant: _____ I hereby guarantee: the accuracy of the information in the registration dossier, not to violate the exclusive rights of third parties to an invention or utility model, the adequacy of translations of quality control methods, instructions for medical use of a pharmaceutical product; submit samples of medicinal products, standard samples of medicinal substances and their impurities in quantities sufficient for threefold analysis, specific reagents, consumables used in the testing of medicinal products (in exceptional cases and on terms of return), as well as their compliance with regulatory documents submitted for registration. I undertake to report all changes in the registration dossier, as well as to submit materials if adverse reactions are detected when using a pharmaceutical product that were not previously specified in the instructions for medical use.		
Date		
Surname, name, patronymic and position of the responsible person of the Applicant		
Signature		

Appendix 2
to the Rules of temporary state
registration of vaccines against
COVID-19

Footnote. The text in the upper right corner of Appendix 2 as amended by the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

The list of documents submitted for temporary state registration of vaccines for manufacturers of the Republic of Kazakhstan

Footnote. The list - as amended by the resolution of the Government of the Republic of Kazakhstan dated 23.09.2021 No. 668 (shall be enforced from the day of its first official publication.).

№	Names of documents
1	2
Part I General documentation*	

IA1.	For production in the territory of the Republic of Kazakhstan - a notarized GMP certificate (if any). For production based on the transfer (transfer) of the full cycle or part of production and technological processes - a notarized GMP certificate.
I A2.	A copy of the state license for pharmaceutical activities (notarized)
I A3.	Appendix to the license
I A4.	If several manufacturers are involved in the production process, the documents of paragraphs IA2, IA3, IA4 are submitted for all production participants
I A5.	Licensed agreement (contract) for the right of production (before the expiration of the patent for the original drug) (if any)
I A6.	A notarized copy of the security document for the invention or useful model of the original medicinal product (submitted by the patent holder of the security document), the security document for the trademark (if any)
I A8.	A document confirming the quality of the finished product of three series (analysis certificate, analysis protocol), one series of which coincides with a series of a sample of the drug submitted for registration
I A 9.	Prion security document for animal substances from the manufacturer
1.B.3.	The text of the labeling for primary and secondary packages, stickers, labels in Kazakh and Russian
Part II Chemical, pharmaceutical and biological documentation*	
II	Content
II A	Composition
II A 1	Qualitative and quantitative composition of the drug (active, excipients)
II A 2	A document confirming the quality of the packaging and sealing materials of the finished product
II A 3	Pharmaceutical development (description of APS, excipients, development of the drug, development of the production process, compatibility of components, surplus, stability, microbiological purity)
II B	Information about production:
II B 1	Production formula
II B 2	Description of production technology
II B 3	Control in the production process (operational control)
II C	Methods for monitoring the source materials
II C 1	Active substance
II C 1.1	A document confirming the quality of the active substance of three series (certificate of analysis of the substance from the manufacturer, analysis protocol, analytical passport)

II C 2	Excipients
II C 2.1	Quality certificates for excipients
II C 3	Packaging material (primary and secondary packaging)
II C 3.1	Certificates of the quality of packaging material with the application of documents governing their quality
II D	The quality control methods of intermediate products (if necessary)
II E	Specification of the quality and methodology of controlling the finished product
II E 1	The regulatory document of the manufacturer for quality control and safety of the drug in electronic form in the "PDF" and (or) "DOC" format, an explanatory note to it
II E 2	Validation of testing methods for the drug*
II F	Stability test results for a period of at least 3 (three) months**
II H	Animal control data
II L.	Additional information confirming quality (if necessary)
Part III. Pharmacological and toxicological documentation	
III.	Content
III A.	Data on toxicity (acute and chronic), (medical immunobiological drug - toxicity with a single introduction and introduction of repeated doses)
III B.	Impact on reproductive function
III C.	Data on embryotoxicity and teratogenicity
III D.	Data on mutagenicity (if any)
III E.	Data on carcinogenicity (if any)
III F.	Pharmacodynamics (for medical genetically biological preparations - the results of a study of reactogenicity)
III G.	Pharmacokinetics (for medical immunobiological drugs - the results of specific activity)
III H.	Data on local irritating effects (for medical immunobiological drugs - the results of the study of immunogenicity)
III Q.	Additional information confirming security (if necessary)
Part IV. Clinical documentation ***	
IV.	Content
IV A.	Clinical pharmacology data (pharmacodynamics, pharmacokinetics)
IV B	Clinical, immunological efficiency
IV C	Diagnostic efficiency
IV D	The results of clinical studies (tests), including preclinical research reports, intermediate reports of the I - II phases of clinical studies

IV D1	Data of post-registration experience (if any)
IV E	Additional information confirming the efficiency
	For production based on the transfer (transfer) of the full cycle or part of production and technological processes, the registration dossier is additionally attached with: 1) an agreement on the transfer of production and technological processes between the manufacturer in the Republic of Kazakhstan and the foreign manufacturer; 2) a report on the results of the transfer made, including a description of the transfer project, the scale of the transfer, critical parameters obtained by the main and additional sites, the final conclusions of the transfer, with the application of the notarized GMP certificate (indicating the date and results of the last inspection of the foreign manufacturer), corresponding to the proper production practice (GMP) of the Republic of Kazakhstan; 3) a report of validation of production processes at the production site in the Republic of Kazakhstan ****; 4) documents confirming that the quality of the source materials (active substance, excipients) used on the production site in the Republic of Kazakhstan does not affect the process or finished product; 5) documents from the manufacturer confirming that the quality control of drugs produced both at the foreign production site and on the production site in the Republic of Kazakhstan is carried out according to one specification; 6) reports of preclinical research; 7) reports of the I - II phases of clinical research and the intermediate report of the III phase of clinical studies conducted with the inclusion of at least 50 (fifty) % of the research subjects provided for by the protocol of the clinical study from the transferring side; At that, the receiving side does not need to conduct the repeated preclinical and clinical studies in the Republic of Kazakhstan; 8) the results of the studies of accelerated stability and at least 6 (six) monthly studies of long-term stability for the receiving side containing a program of stability studies indicating the series of the drug from the transferring side; 9) the post-registration obligations of the transferring side on the presentation of stability data from the sites of the transferring and receiving sides (the frequency of the presentation of information according to the program for the study of stability). With the full or partial transfer (transfer) of production and technological processes, the applicant ensures the full compliance of the production conditions and the quality assurance system at the production site in the Republic of Kazakhstan with the production conditions

	and the system for ensuring the quality of the production site outside the territory of Kazakhstan.

Note:

* For pharmacopeic techniques, verification data are presented;

** In the event of emergency situations of a natural or technogenic nature and eliminating their consequences, organization and conduct of sanitary-anti-epidemic and sanitary-preventive measures and the related restrictive measures, including quarantine, a domestic producer of a vaccine against Covid-19 when making changes to the registration dossier provides the following:

the results of stability studies conducted in the manner prescribed by the Rules for the Medicine Stability, Storage and Re-Control of drugs, approved by the order of the Minister of Health of the Republic of Kazakhstan dated October 28, 2020 No. ҚР ДСМ 165/2020 (registered in the Register of state registration of regulatory legal acts under No. 21545), in 1 (one) month after the release of 3 (three) consecutive industrial series;

a guarantee obligation to provide the results of stability studies conducted after 3 (three) and 6 (six) months for 3 (three) consecutive industrial series after the completion of stability studies.

*** the approved research protocol, the approved study report, the permission of the state body to conduct a study (if any), the approval of the ethical commission, a copy of the sponsor liability agreement and (or) the research center, in the event of harm to the life and health of the subject of the study, a copy of individual registration maps of the subjects of the study (for international, multicenter clinical studies of 20%), chromatograms (when providing a study of bioequivalence), copies of contracts between the sponsor of clinical research and the research center (contract research organization) (if necessary after the removal of confidential information); the approved research protocol, the approved study report, the permission of the state body to conduct a study (if any), the approval of the ethical commission, a copy of the sponsor liability agreement and (or) the research center, in the event of harm to the life and health of the subject of the study, a copy of individual registration cards of the subjects of the study (for international, multicenter clinical studies - 20%), chromatograms (when providing a study of bioequivalence), copies of contracts between the sponsor of clinical research and the research center (contract research organization) (if necessary after the removal of confidential information);

**** a warranty obligation to submit a report on the validation of production processes conducted on 3 (three) consecutive industrial series within 7 (seven) days after the completion of validation.

Appendix 3
to the Rules of temporary
state registration of
vaccines against
COVID-19

Footnote. Appendix 3 as amended by the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

Conclusion on the safety, quality and effectiveness of the vaccine

1. The expert commission reports the results of the examination for safety, quality and effectiveness of the vaccine for the purposes of temporary state registration in the Republic of Kazakhstan:

Number and date of application	
The trade name of the vaccine (indicating the dosage form, dosage, concentration and volume of filling, the number of doses in the package for the drug)	
Organization-manufacturer, country-manufacturer, holder of a temporary registration certificate	
The conclusion of the expert commission (positive or negative)	

2. Conclusion (positive): materials and documents of the registration dossier to the vaccine presented for temporary state registration in the Republic of Kazakhstan, meet the requirements of the Rules of temporary state registration of vaccines against Covid-19 (hereinafter - the Rules).

The vaccine (the commercial name of the vaccine indicating the dosage form, dosage, concentration and volume of filling, the number of doses in the package) may be registered in the Republic of Kazakhstan for a period of 18 (eighteen) months.

Conclusion (negative): materials and documents of registration dossier to the vaccine presented for temporary state registration in the Republic of Kazakhstan do not meet the established requirements of the Rules.

The vaccine (the commercial name of the vaccine indicating the dosage form, dosage, concentration and volume of filling, the number of doses in the package) may not be registered in the Republic of Kazakhstan.

Head of the expert commission

_____ _____

signature name, surname, patronymic (if any)

Members of the expert commission

_____ _____

signature name, surname, patronymic (if any)

_____ _____

signature name, surname, patronymic (if any)

_____ _____

signature name, surname, patronymic (if any)

Appendix 4
to the Rules of temporary
state registration of

vaccines against
COVID-19

Footnote. Appendix 4 as amended by the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

Form

Coat of arms of the Republic of Kazakhstan
Ministry of Health of the Republic of Kazakhstan
Temporary registration certificate РК-БП - №_____

1.	Name of the holder of the registration certificate	
2.	Country of the holder of the registration certificate	
To certify that the drug is registered and allowed for use in medical practice in the territory of the Republic of Kazakhstan (information on a registered drug)		
3.	Trade name of the drug	
4.	For manufacturers, the trade name for exports	
5.	International nonproprietary name (if any)	
6.	Dosage form	
7.	Dosage	
8.	Packing	
9.	The code of anatomical and therapy-chemical classification	
10.	The composition of active substances	
11.	Shelf life	
12.	The issue procedure (by prescription, no prescription)	

Information about the manufacturer of the drug

№	Type of organization or production site	Name of organization	Country
1.	Manufacturer		
2.	Packer		

The date of temporary state registration "___" _____ 20___ No. _____ of the decision.

Valid until ____ _____ 20___.

FULL NAME (if any) of the head of the state body (or authorized person)

Medical use of vaccines that received a temporary registration certificate on a voluntary basis is allowed, in the presence of reports on the I - II phases of clinical research and intermediate report of the III phase of research conducted with the inclusion of at least 50 (fifty) % of the research subjects provided for by the protocol of clinical research.

Appendix 5

to the Rules of temporary
state registration of
vaccines against
COVID-19

Footnote. The Rules are supplemented by Appendix 5 in accordance with the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

Form

Application for amendments to the registration dossier of the vaccine

1.	Trade name	in Kazakh	
		in Russian	
		in English	
2.	International nonproprietary name	in Kazakh	
		in Russian	
		in English	
3.	Dosage form	in Kazakh	
		in Russian	
4.	Dosage (concentration) (filled out if any, the volume is filled in the package)	The concentration is indicated for liquid, soft and gaseous dosage forms	
5.	Anatomical and therapy-chemical classification	Code	
		Name in Kazakh	
		Name in Russian	
6.	Methods of introduction		
7.	Packaging (fill out a list of values)		

№	Form (primary or secondary)	Name	Size (if any)	Volume (if any)	Number of units in a package	Brief description
1)	Primary					
2)	Intermediate (if any)					
3)	Secondary					
4)	Barcode of secondary packaging (GTIN) (if any)	Indicate the barcode for each dosage (concentration)				
8.	Full qualitative and quantitative composition (a list of values is filled out)					

				Normative document regu					

№	Type of substance (active or excipient)	Name	Number per unit of dosage form	latin g the qual ity, or phar mac opei a indi cati ng the year of publ icati on	Manufacturer, country and address of the production site (for active substances)	Controlled by the International Committee for Drug Control (noted if any)	The presence of toxic substances (noted if any)	Wild or cultivated (for medicinal plant material) and the place of growth	A sign of human or animal origin (noted if any)
1)	Active					II tab. III tab. IV tab.	1-list 2-list		
2)	Excipient								

9.	Shelf live of the drug	The proposed shelf life	
		The proposed period of application (after the first opening of the container)	
		The proposed period of application (after dissolution or dilution)	
10.	Transportation conditions		
11.	Storage conditions	The proposed storage conditions	
		The proposed storage conditions after the first opening of the packaging	

12.	Security document for an invention or useful model, trademark (if any)			
	Name of security document	№ of security document	Date of issue	Time period for issuing
13.	Production	1) completely at this production; 2) partly at this production; 3) completely at other production		
14.	The manufacturer (s) of the drug and the site (s) of production (including areas of production of any component (including a solvent of the dosage form), which is part of the drug)			

			№, date and vali				Name, surname,	Name, surname, patronymic

№	Type of manufacturer	Name, country (in Kazakh, Russian, English)	dity of the permits	Legal address	Actual address	Telephone, fax, e-mail	patronymic (if any), position of the head	(if any), position of the contact person
1)	Manufacturer							
2)	Enterprise–packer							
3)	Primary							
4)	Secondary							
5)	Quality control manufacturer							
6)	Manufacturer responsible for the release of the series							
7)	License holder		Data on production license issued by the authorized body of the country of the manufacturer					

8)	Holder of the registration certificate							
9)	Applicant or representative office		Data on power of attorney					
10)	Authorized person for implementation of the pharmacological control in the Republic of Kazakhstan							

15.	Laboratory of the country-manufacturer for quality control of blood products and vaccines, responsible for quality control (release of series)		
1)	Name of laboratory		
2)	address of the place of activity		
3)	Country		
4)	tel/fax		
5)	e- mail		
16.	Changes made to the registration dossier of the drug (indicate the changes made)		
	Type of changes	Before changes	The changes made
17.	Data on the contract for examination of drugs		
1)	№ of contract		
2)	Date of conclusion		
3)	Period of validity		
18.	Subject that paid for the examination		
1)	Name		
2)	Country		
3)	Legal address		
4)	Actual address		
5)	FULL NAME. (if any), position of the head		
6)	Telephone		
7)	Fax		
8)	E-mail		

9)	Business identification number	
10)	Individual identification number	
11)	Bank	
12)	Operating account	
13)	Foreign currency account	
14)	The code	
15)	Bank identification code	

Applicant: _____

I guarantee the reliability of the information of the registration dossier, not to violate exclusive rights by third parties to the invention or useful model, the adequacy of translations of quality control methods, instructions for the medical use of the drug; present samples of drugs, standard samples of medicinal substances and their impurities in quantities sufficient for three-fold analysis, specific reagents, consumables used in the testing of drugs (in exceptional cases and on return conditions), as well as their compliance with regulatory documents submitted for registration.

I undertake to report all changes to the registration dossier, as well as present materials when unwanted reactions are detected when using a drug that previously not specified in the instructions for medical use.

Date	
Full name and position of the executive person and the applicant	
Signature	

Appendix 6
to the Rules of temporary
state registration of
vaccines against
COVID-19

Footnote. The Rules are supplemented by Appendix 6 in accordance with the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244; as amended by the resolution of the Government of the Republic of Kazakhstan dated 17.08.2022 No. 566 (shall enter into force from the day of its first official publication).

Form

List of changes made to the registration dossier of the vaccine

A. Administrative changes

A.1 Changing the name and (or) address of the holder of the registration certificate	Conditions	Documents and data	Procedure
a) the holder of the registration certificate does not change	1	1, 2	IA
б) changing the holder of the registration certificate		2, 3, 4	IB

Conditions

1. The holder of the registration certificate is a legal entity.

Documentation

1. A document of an authorized body or authorized organization (for example, a tax authority), which contains a new name or address.
2. Revised information about the drug (updated brief description of the drug, medical instructions (leaf-liner), labeling).

3. A brief description of the pharmacological control system from the new holder of the registration certificate (HRC) includes the following elements:
- information that the HRC has at his disposal a person responsible for the global pharmacological control;
- contact details of the person responsible for global pharmacological control;
- a declaration signed by the HRC that he has a pharmacological control system for performing tasks and duties on post-registration control of safety of drugs;
- link to the place (address) where the master file of the pharmacological control system is stored.
4. Contractual relationships between the manufacturer and the HRC for the right to carry out activities on the pharmacological control.

A.2 Changing (trade) name of the drug	Conditions	Documents and data	Procedure
Drugs	1	1, 2, 3, 4, 5	IB

Conditions
1. Confusion should be avoided with the names of existing medications or the international nonproprietary name INN, if the name is generally accepted, the change should be made in the following order: from the generally accepted name to the pharmacopeial or to INN

Documentation
1. Motivated justification of the need to change the name of the drug.
2. Revised information about the drug (updated brief characteristics of the drug, medical use instructions (leaf-liner), labeling).
3. A copy of the document issued by the competent authorities of the country-manufacturer, which certifies a change in its name.
4. The signed declaration that the place, method, composition, regulatory document regulating the quality of the drug remained unchanged.
5. The statement of the changes to the approved regulatory document on quality control and safety of the drug.

A.3 Changing the name of active pharmaceutical substance or excipient	Conditions	Documents and data	Procedure
	1	1, 2	IA

Conditions
1. Pharmaceutical substance and excipient are not changed.

Documentation
1. Certificate of the World Health Organization (hereinafter - WHO) on approval or a copy of the list of an international nonproprietary name. If the confirmation is applicable that the change corresponds to the state pharmacopoeia of the Republic of Kazakhstan. The declaration that the name of plant drugs of plant origin corresponds to the documents of the Republic of Kazakhstan.
2. Revised information about the drug.

A.4 Changing the name and (or) addresses: the manufacturer (including, if applicable, quality control sites) or the holder of the master file of an active pharmaceutical substance (hereinafter referred to as MFAPS), or the supplier of active pharmaceutical substance, source materials, reagents or intermediate products used in production of active pharmaceutical substance (if indicated in the technical dossier), if the registration dossier does not have certificates of conformity PH. Eur., or manufacturer of a new auxiliary substance (if indicated in the technical dossier)	Conditions	Documents and data	Procedure
	1	1, 2, 3	IA

Conditions 1. Production site and none of the production operations is changed.				
Documentation 1. A document from an authorized body (for example, a tax authority) or an authorized organization that indicates a new name and (or) address. 2. A change to the corresponding section (s) of the dossier. 3. When changing the name of the holder of the MFAPS – an updated permission to access.				
A.5 Changing the name and (or) address of the manufacturer of the drug, including production sites and quality control sites		Conditions	Documents and data	Procedure
a) the actions for which the manufacturer (importer) is responsible, include the release of the series		1	1, 2, 3	IA
b) the actions for which the manufacturer/ importer is responsible, do not include the release of series		1	1, 2, 3	IA
Conditions 1. There is no change in the production process, the actual location of the site, the regulatory document on quality control and safety of the drug.				
Documentation 1. A copy of the corrected permission for production (if any) or a document from an authorized body or authorized organization, which mentions a new name and (or) address. 2. If applicable, the change to the corresponding section (s) of the dossier, including the revised information about the drug. 3. The updated brief characteristics of the drug, the instructions for medical use (leaf-liner), labeling.				
A.6	Change of the code of anatomical and therapy-chemical (hereinafter-ATC) classification	Conditions	Required documentation	Type of procedure
		1	1, 2	IB
Conditions 1. Change due to approval or change of ATC code by WHO.				
Documentation 1. Certificate of WHO for approval or a copy of the list of codes of the ATC. 2. Revised information about the drug (updated brief characteristics of the drug).				
A.7	Exclusion of the production site (including for active pharmaceutical substance, intermediate products , a drug, a packager, a manufacturer responsible for the release of a series, quality control of the series or supplier of the source material, reagent or excipient (	Conditions		Type of procedure

if indicated in the dossier)		Required documentation	
	1, 2	1, 2	IA
Conditions 1. At least one previously approved production site/manufacturer remains, which carries out the same functions as those to be excluded. If applicable, in the Republic of Kazakhstan at least one manufacturer remains responsible for the release of series capable to certify the test of product in order to release series in the Republic of Kazakhstan. 2. An exception is not a consequence of critical shortcomings of production.			
Documentation 1. In the form of an application for changes, it is necessary to clearly indicate the “current” and “proposed” manufacturers listed in the registration application. 2. The change to the corresponding section (s) of the dossier, including the revised information about the drug.			
A.8 Changing the audit date for verification of the compliance of the manufacturer of active pharmaceutical substance to the Rules of proper production practice of the Republic of Kazakhstan	Conditions	Required documentation	Type of procedure
		1	IA
Documentation 1. Written confirmation of the manufacturer of the drug containing an indication of verification of the compliance of the manufacturer of active pharmaceutical substance to the Rules of proper production practice of the Republic of Kazakhstan.			

Б. Change of the quality

Б.I Active pharmaceutical substance

Б.I. a) production

Б.I.a.1 A change in the manufacturer of the source material/reagent/ intermediate product used in the process of production of active pharmaceutical substance (APS), or a change in the manufacturer of the APS (including, if applicable, quality control sites), if there is no certificate of compliance with the European pharmacopei in the registration dossier.	Conditions	Required documentation	Type of procedure
a) the proposed manufacturer belongs to the same pharmaceutical group as the approved manufacturer	1, 2, 3	1, 2, 3, 4, 5, 6, 7, 9	IB
b) the introduction of a new manufacturer of an	-		II

active pharmaceutical substance, justified by MFAPS		-	
c) the proposed manufacturer uses a sharply different method of synthesis or production conditions that change important indicators of the quality of active pharmaceutical substance, such as a qualitative and (or) quantitative profile of impurities that requires qualifications, or physico-chemical properties that affect bioavailability	-	-	II
d) A new manufacturer of material requiring the assessment of viral safety and (or) risk of transmissive spongyform encephalopathy (hereinafter - TSE)	-	-	II
e) The change affects the biological active pharmaceutical substance or source material/reagent/ intermediate product used in the production of a biological/immunological drug	-	-	II
f) a change in the procedure for quality control of active pharmaceutical substance: changing or adding the site on which the control/test of the series is carried out	2, 4	1, 5	IB
g) the introduction of a new manufacturer of an active pharmaceutical substance that does not have MFAPS and requires a significant update of the corresponding section of the dossier according to an active pharmaceutical substance	-	-	II
h) the inclusion of an alternative platform for			

sterilization of an active pharmaceutical substance using the method of state pharmacopei of the Republic of Kazakhstan	-	1, 2, 4, 5, 8	IB
i) introduction of a new site for micronization	2, 5	1, 4, 5, 6	IB
j) changes in the testing of quality control of biological active pharmaceutical substance: replacing or inclusion of the site on which the control/testing of the series is carried out, including the biological/immunological/ immuno-chemical method	-	-	II
k) a new site for storage of the main bank of cells and (or) working banks of cells	-	1, 5	IB

Conditions

1. Specifications of the source materials and reagents (including intra-production controls, methods of analysis of all materials) are identical to previously approved. Specifications (including intra-production control, methods of analysis of all materials), methods of preparation (including the size of the series) and a detailed way of synthesis of intermediate products and active pharmaceutical substances are identical to previously approved.

2. Active pharmaceutical substance is not biological/ immunological or sterile.

3. If the materials of human or animal origin are used in the production process, the manufacturer does not use a new supplier, in relation to whom a viral security assessment is required and compliance with the state pharmacopoeia of the Republic of Kazakhstan on minimizing the risk of transmitting agents of spongyform encephalopathy of animals through drugs for medical and veterinary use.

4. The transfer of the method from the old to the new site was made successfully.

5. Specification for the size of particles of active pharmaceutical substance and the corresponding analytical method do not change.

Documentation

1. If applicable, the change to the corresponding section (s) of the dossier.

2. The declaration of the HRC or the holder of the MFAPS respectively, that the procedures of quality control of the method of synthesis (or for plant drugs, respectively): the method of preparation, geographical source, the production of plant pharmaceutical substance and the production process) and the specification of active pharmaceutical substance and the source material/reagent/intermediate product in the production process of an active pharmaceutical substance (if applicable) do not differ from the previously approved.

3. Either a certificate of conformity of the European Pharmacopeia for TSE for any new source of material, or (if applicable) documentary confirmation that the source of the material subjected to the risk of TSE was previously studied by the authorized body; and its compliance with the State Pharmacopoeia of the Republic of Kazakhstan was confirmed on the minimization of the risk of transmitting agents of spongyform encephalopathy of animals through drugs for medical and veterinary use was confirmed. The following information must be presented: the name of the manufacturer; the type of animals and fabrics from which the material is made; the country of the origin of animals, its use and acceptability in the past.

4. The data of the analysis of the series (in the format of the comparative table) of at least two series (at least, experimental-industrial) of active pharmaceutical substance from current and offered manufacturers/sites.

5. In the form of an application for changes, it is necessary to clearly define the “current” and “proposed” manufacturers as indicated in section 2.5 of the application form.

6. If the active pharmaceutical substance is used as the source material, the declaration of the qualified person of each holder of the production license specified in the application and the qualified person of each holder of the production license specified in the application as responsible for the release of the series. In declarations, it is necessary to indicate that the manufacturer (s) of active pharmaceutical substance, specified in the application, carries out their activity in accordance with the Rules of proper production practice of the Republic of Kazakhstan in relation to the source materials. Under certain circumstances, it is allowed to submit one declaration (see note to change Б.II.б.1).

7. Warranty letter (if necessary) of the manufacturer of an active pharmaceutical substance should notify the holder of the registration certificate of any changes in the production process, specifications and analytical methods of active pharmaceutical substance.

8. Confirmation that the proposed site is properly licensed in relation to the drug form under consideration, drug or production operation.

9. Comparative data (in the form of a table) of the synthesis methods and specifications of the quality of active pharmaceutical substance and the source material/reagent/intermediate product in the production process of the active pharmaceutical substance of the proposed and approved manufacturer.

Б.I.а.2 Changes in the production process of active pharmaceutical substance	Conditions	Required documentation	Type of procedure
a) a non-essential change in the production process of active pharmaceutical substance	1, 2, 3, 4, 5, 6, 7	1, 2, 3	IB
b) a significant change in the process of production of active pharmaceutical substance, which can have a significant effect on the quality, safety or effectiveness of the drug	-	-	II
c) the change affects the biological/ immunological substance or the use of another substance obtained by chemical synthesis in the production of a biological/ immunological drug, which can have a significant effect on the quality, safety or effectiveness of the drug and is not associated with the protocol	-	-	II
d) the change affects the plant drug, namely: geographical source, method of production or preparation	-	-	II
e) non-significant change in the closed part of the MFAPS	-	1, 2, 3, 4	IB
Conditions			

1. There is no undesirable change in the qualitative or quantitative profile of impurities or physico-chemical properties. 2. The method of synthesis remains the same, that is, intermediate products do not change and new reagents, catalysts or solvents are not introduced into the process. Geographical source, the preparation of plant materials and the method of production of medicinal plant drugs do not change. 3. Specifications of active pharmaceutical substance and intermediate products do not change. 4. The change is completely described in the open part (part of the "applicant") of the MFAPS (if applicable). 5. Active pharmaceutical substance is not a biological/ immunological substance. 6. The change does not affect the geographical source, the method of production or preparation of a medicinal plant drug. 7. The change does not affect the closed part of the MFAPS.			
Documentation 1. The change to the corresponding section (s) of the dossier, including a direct comparison of the current and new processes. 2. The data of the analysis of the series (in the format of the comparative table), at least two series (at least, experimental-industrial), made using the approved and proposed processes. 3. Copies of approved specifications of active pharmaceutical substance. 4. The declaration of HRC or the holder of the MFAPS respectively, that there is no change in the qualitative and quantitative profile of impurities or physico-chemical properties, the method of synthesis, the specifications of the active pharmaceutical substance and intermediate products do not change.			
Note	to Б.I.a.2.б) Significant changes in active pharmaceutical substances obtained by chemical synthesis include changes in the method of synthesis or production conditions, which are able to change important indicators of the quality of active pharmaceutical substance, such as qualitative and (or) quantitative profile of impurities that requires qualifications, or physical and chemical properties, affecting bioavailability.		
Б.I.a.3 Changes in the size of the series (including the range of the size of the series) of an active pharmaceutical substance or an intermediate product used in the production process of an active pharmaceutical substance	Conditions	Required documentation	Type of procedure
a) an increase in the size of the series up to 10 times compared to the registered size	1, 2, 3, 4, 5, 6, 7, 8	1, 2, 5	IB
b) 10-fold fragmentation	1, 2, 3, 4, 5	1, 2, 5	IB
c) the change requires the analysis of the comparability of biological /immunological active pharmaceutical substance	-	-	II
d) an increase in the size of the series more than 10 times compared to the registered size	-	1, 2, 3, 4	IB
e) an increase/decrease in the scale of production of			

biological/immunological active pharmaceutical substance without changing the production process (for example, duplication of the line)	-	1, 2, 3, 4	IB
Conditions 1. All changes in production methods affect only those necessary for enlargement or fragmentation, for example, the use of equipment of a different size. 2. It is necessary to present the test results according to the specifications of at least two series of the proposed size of the series. 3. The drug under consideration is not a biological/immunological drug. 4. The change does not make an undesirable affect on the reproduction of the process. 5. Change should not be a result of unforeseen situations that arose during production, or violations of stability. 6. Specifications of active pharmaceutical substance/intermediate products do not change. 7. Active pharmaceutical substance is not sterile. 8. The size of the series is within the limit of a 10-fold range of the size of the series provided for the registration, or after a subsequent change that was not a change in IA type.			
Documentation 1. The change to the corresponding section (s) of the dossier. 2. The numbers of series tested series have the proposed size of the series. 3. The data of the analysis of the series (in the format of the comparative table), at least one industrial series of active pharmaceutical substance or intermediate product, respectively, produced in the approved and proposed size. At the request, it is necessary to submit data on the following two full industrial series; the holder is obliged to inform if the results of the analysis do not fit into the specification and offer an action plan. 4. Copies of approved specifications of active pharmaceutical substance (and intermediate products, if applicable) . 5. The declaration of the HRC or the holder of the MFAPS respectively, that all changes in production methods affect only those necessary for enlargement or fragmentation, for example, the use of equipment of a different size; a change does not make an undesirable affect on the reproduction of the process; a change is not a consequence of unforeseen situations that arose during production, or violations of stability; specifications of active pharmaceutical substance/intermediate products do not change			
Б.I.a.4 Changes in intra-production tests or acceptability criteria used in the production of active pharmaceutical substance	Conditions	Required documentation	Type of procedure
а) tightening intra-production criteria for acceptability	1, 2, 3, 4	1, 2	IA
б) adding new intra-production tests or acceptance criteria	1, 2, 5, 6	1, 2, 3, 4, 6	IA
в) exclusion of an insignificant intra - production test	1, 2, 7	1, 2, 5	IA
г) expansion of approved intra-production criteria for acceptability, which			II

significantly affect the total quality of active pharmaceutical substance			
д) exclusion of an intra-production test, which can significantly affect the total quality of active pharmaceutical substance			II
e) adding or replacing an intra-production test for security or quality reasons		1, 2, 3, 4, 6	IB
Conditions 1. A change is not a consequence of any obligation adopted based on the results of previously conducted examinations in order to analyze the criteria for acceptance of the specification (for example, during registration or changes of II type). 2. A change is not a consequence of unforeseen situations that arose during production, for example, a new unskilled admixture, a change in the limits of the content of impurities. 3. Any change should be adjusted to the range of acting approved acceptability criteria. 4. The analytical technique does not change or changes slightly. 5. No new testing method is based on a new non-standard methodology or standard methodology used in a new way. 6. The new testing method is not a biological/immunological/immunochemical or method that uses a biological reagent for a biological active pharmaceutical substance (with the exception of standard pharmacopeic microbiological methods). 7. The specification parameter does not affect the critical parameter, for example, any of the following: quantitative definition, impurities (unless a certain solvent is unambiguously used in the production of active pharmaceutical substance), any critical physical characteristics, for example, the size of the particles, the bulk density before and after the compaction, test for authenticity, water, any request to change the frequency of tests.			
Documentation 1. The change to the corresponding section (s) of the dossier. 2. Comparative table of current and proposed intra-production tests. 3. A detailed description of the new non-pharmacopeial analytical methodology and validation data (in appropriate cases). 4. The data of analysis of two industrial series (for biological active pharmaceutical substances, in the absence of proper justifications - three industrial series) of active pharmaceutical substance in all parameters of the specification. 5. Rationale /assessment of risks from the HRC or the holder of the MFAPS, respectively, confirming that the intra-production parameters are insignificant or outdated. 6. Rationale from the HRC or the holder of the MFAPS, respectively, of new intra-production tests and limits.			
B.I.a.5 Amendment in the active substance of the vaccine against coronavirus COVID-19 caused by SARS-CoV-2	Conditions	Required documentation	Procedure type
a) replacement or addition of a new serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences			II
Documentation required for the examination of modified vaccines:			

1) cover letter with motivating justification;
2) amendment to the relevant section (s) of the dossier;
3) updated quality documents:
by drug substance:
general information of the active substance: name, structure, general properties;
manufacturer, description of the manufacturing process and its control;
control of raw materials;
control of critical stages and intermediate products;
process validation and/or evaluation;
development of the production process;
proof of structure and characteristic;
impurities;
quality specification;
analytical procedures;
validation of analytical methods;
document confirming the quality of the active substance of three batches (certificate of analysis of the substance from the manufacturer, analytical protocol, analytical passport);
justification of the specification;
reference standards or substances;
packing (closure) system;
summary of stability and conclusions;
post-authorization stability protocol and stability commitment;
stability data;
by finished product:
a document confirming the quality of the finished product of three batches (certificate of analysis, analytical protocol), one batch of which coincides with the batch of the drug product sample submitted for registration;
a document on prion safety for substances of animal origin from the manufacturer (supplier);
qualitative and quantitative composition of the medicinal product (active, excipients);
a document confirming the quality of the packaging and closing materials of the finished product;
pharmaceutical development (description of API, excipients, drug product development, manufacturing process development, compatibility of components, excesses, stability, microbiological purity);
production formula;
description of production technology;
control during production (operational control);
control methods of starting materials;
quality certificates for excipients;
Intermediate quality control methods (if any)
the manufacturer's regulatory document on quality control and safety of the medicinal product in electronic form in .docx format;
validation of drug product test methods;
Stability results of at least 1 month on at least three pilot batches with a warranty obligation to provide the results of stability studies conducted at 3 (three) and 6 (six) months on 3 (three) consecutive production batches after completion of stability studies;
additional information confirming the quality (if any);
4) guarantee letter of the temporary marketing authorization holder (in any form) on conducting a clinical study of the immunogenicity of the variant vaccine after obtaining temporary registration.
Immunogenicity data of monovalent and polyvalent variant vaccine against variant strain (s) are evaluated based on the presented data:
clinical study of immunogenicity in primary vaccination with a variant vaccine (it is recommended to conduct at least one trial in subjects not previously vaccinated and without signs of previous infection);

a clinical study of immunogenicity in vaccination with a variant vaccine (single dose) of subjects who had previously received primary vaccination with a parent (baseline) vaccine;

. the titers of neutralizing antibodies measured with respect to the corresponding vaccine strain (s), that shall be, in the parent group of the vaccine against the parent strain and the variant group against the variant strain (s);

that the lower limit of the 95% confidence interval of the difference in seroconversion levels for the vaccine with the variant strain compared to the parent strain shall not exceed 10% (seroconversion is defined as a 4-fold increase in titer from state to vaccination to state of vaccination);

on evidence that variant vaccines shall be produced by the same manufacturer using the same process as the original vaccines, the clinical efficacy of which has been demonstrated for a modified vaccine (an altered variant (strain) used in inactivated vaccines or an altered variant of a protein, mRNA or other subdivision);

according to a detailed description of the strain or protein itself, mRNK or other subunit with fixation of differences from the original version (comparative characterization of strains or subunits);

on the safety of the variant vaccine collected during immunogenicity tests.

The documentation is submitted taking into account the EMA/117973/2021 guidelines on regulatory requirements for vaccines designed to protect against the changed strain (s) of SARS-CoV-2 and EMA/175959/ 2021, on guidelines for updating variant strains for vaccines designed to protect against human coronavirus.

Б.I. б) Quality control of the active pharmaceutical substance

Б.I.б.1 Changing the specification parameters and (or) acceptance criteria of an active pharmaceutical substance, source material / intermediate product / reagent used in the production process of an active pharmaceutical substance	Conditions	Required documentation	Type of procedure
а) tightening the acceptance criteria for the specification of drugs, subject to release of series by the official control body	1, 2, 3, 4	1, 2	IA
б) tightening of specification acceptance criteria	1, 2, 3, 4	1, 2	IA
в) adding a new parameter and the corresponding test method to the specification	1, 2, 5, 6, 7	1, 2, 3, 4, 7	IB
г) exclusion of a minor specification parameter (e.g. exclusion of an outdated parameter)	1, 2, 8	1, 2, 6	IA
д) exclusion of a specification parameter that can significantly affect the overall quality of the active pharmaceutical substance and (or) drug			II
е) a change that is beyond the approved range of acceptance criteria for			II

specifications of the active pharmaceutical substance			
ж) extension of the approved specification acceptance criteria for source materials/ intermediate products that significantly affect the total quality of the active pharmaceutical substance and (or) drug			II
з) addition or replacement (excluding biological and immunological substance) of a specification parameter and its corresponding test method for reasons of safety or quality		1, 2, 3, 4, 5, 7	IB
и) if there is no article of the State Pharmacopoeia of the Republic of Kazakhstan for the active pharmaceutical substance, changing its own specification data to the data of an unofficial pharmacopoeia or a pharmacopoeia of a third country		1, 2, 3, 4, 5, 7	IB
Conditions 1. The change is not a consequence of any obligation made as a result of previous examinations in order to revise the acceptance criteria for the specification (for example, during registration of a drug or introduction of changes of II type). 2. The change is not a consequence of unforeseen situations that arose during production, for example, a new unqualified impurity, a change in the limits for the content of the amount of impurities. 3. Any change must be within the range of current approved acceptance criteria. 4. Analytical procedure does not change or changes slightly. 5. No new test method is based on a new non-standard methodology or a standard methodology used in a new way. 6. The new test method is not a biological/immunological/immunochemical method or a method that uses a biological reagent for a biologically active pharmaceutical substance (with the exception of standard pharmacopoeial microbiological methods). 7. Modification of any material does not affect the genotoxic admixture. If an active pharmaceutical substance is involved, with the exception of residual solvents, which must comply with the limits corresponding to the article of the State Pharmacopoeia of the Republic of Kazakhstan, the control of any new impurity must comply with the State Pharmacopoeia of the Republic of Kazakhstan. 8. The specification parameter does not affect a critical parameter, such as any of the following: quantitation, impurities (unless a specific solvent is explicitly used in the manufacture of the active pharmaceutical substance), any critical physical characteristic, such as particle size, bulk density before and after compaction, authentication test, water, any request for a matrixing.			
Documentation			

1. A change to the relevant section (s) of the dossier. 2. Comparison table of current and proposed specifications. 3. Detailed description of any new analytical method and validation data (where appropriate). 4. Data of the analysis of two industrial series (in the absence of a rationale of the contrary for biologically active pharmaceutical substances - three series) of the corresponding active pharmaceutical substance for all specification parameters. 5. In appropriate cases, data of the test for the comparative kinetics of dissolution of a drug containing an active pharmaceutical substance, at least from experimental-industrial series that meets the current and proposed specifications. For herbal medicinal products, comparative disintegration data are sufficient. 6. Rationale/risk assessment by the HRC or holder of the MFAPS, respectively, confirming that the intra-production parameter is not significant or out of date. 7. Rationale by the HRC or holder of the MFAPS, respectively, of the new specification parameter and acceptance criteria.			
Б.I.б.2 Changing the analytical method of the active pharmaceutical substance or source material, intermediate product, reagent used in the process of manufacturing the active pharmaceutical substance	Conditions	Required documentation	Type of procedure
а) changes to an approved analytical method	1, 2, 3, 4	1, 2	IB
б) exclusion of the analytical method of the active pharmaceutical substance or source material, intermediate product, reagent, if an alternative analytical method has already been approved	7	1	IA
в) other changes in the analytical methodology (including replacement or addition) of a reagent that does not significantly affect the total quality of the active pharmaceutical substance	1, 2, 3, 5, 6	1, 2	IB
г) a significant change or replacement of a biological , immunological, immunochemical test method or a method that uses a biological reagent for a biologically active pharmaceutical substance			II
д) other changes in the analytical methodology (including the addition or			

replacement) of the active pharmaceutical substance or source material/ intermediate product		1, 2	IB
Conditions 1. The necessary validation has been performed to confirm that the updated analytical method is at least equivalent to the previous one. 2. The limits of the content of the sum of impurities have not changed, new unqualified impurities have not been detected. 3. The method of analysis has not changed (for example, changing the column length or temperature, but not a different type of column or method). 4. The test method is not a biological, immunological, immunochemical method or a method that uses a biological reagent for a biologically active pharmaceutical substance (with the exception of standard pharmacopoeial microbiological methods). 5. No new test method is based on new non-standard methods or standard methods used in a new way. 6. The active pharmaceutical substance is not biological, immunological. 7. An alternative analytical method for the specification parameter has already been approved, but such a method has not been included through the IA notification.			
Documentation 1. A change to the relevant section (s) of the dossier, including a description of the analytical methodology, a summary of the validation data, revised specifications for impurities (if applicable). 2. Comparative validation results or, if justified, comparative analysis results demonstrating that the current and proposed tests are equivalent. This requirement does not apply if a new analytical method is added.			

Б.I. в) packaging and sealing system

Б.I.в.1 Change in the primary packaging of the active pharmaceutical substance	Conditions	Required documentation	Type of procedure
а) qualitative and (or) quantitative composition	1, 2, 3	1, 2, 3, 4, 6	IA
б) qualitative and (or) quantitative composition for sterile or non-frozen biological/immunological active pharmaceutical substances			II
в) liquid active pharmaceutical substances (non-sterile)		1, 2, 3, 5, 6	IB
Conditions 1. In terms of relevant properties, the proposed packaging material must be at least equivalent to the approved one . 2. Appropriate stability studies have been started in accordance with the established requirements and the applicant, at the time of the introduction of the changes, has analyzed the relevant stability parameters on at least two experimental-industrial series, and he has at his disposal satisfactory results of at least three months of stability studies. However, if the proposed package is more stable than the registered package, then three-month stability data are not required. Upon completion of such studies, if the results are not within the specification, or potentially not within the specification at the end of the expiration date/retest period, they must be submitted to the competent authority immediately, along with a proposed action plan. 3. Sterile, liquid and biological/immunological active pharmaceutical substances are excluded.			

Documentation

1. A change to the relevant section(s) of the dossier.

2. Required data on the new packaging (e.g. comparative data on permeability e.g. for O2, CO2, moisture, etc.), including confirmation that the material complies with the relevant pharmacopoeia requirements for plastic materials and objects in contact with food.

3. In appropriate cases, it is necessary to provide confirmation that the interaction between the contents and the packaging material does not occur (for example, there is no movement of the components of the proposed material into its contents, the components of the medicinal product do not pass into the package), including confirmation that the material meets the relevant pharmacopoeial requirements about plastic materials and objects in contact with food.

4. Declaration of the HRC or the holder of the MFAPS that the required stability studies have been started in accordance with the established requirements (indicating numbers of series); and that (where applicable) the required minimum satisfactory stability data were available at the time of the change; and that the available data did not indicate any problem. Confirmation must also be provided that the studies will be completed and that if the results are not within specification or potentially not within specification at the end of the retest period, expiration date, they will be immediately submitted to the competent authority along with a proposed action plan.

5. Results of stability studies carried out in accordance with established requirements for significant stability parameters on at least two experimental-industrial or industrial series, covering at least three months, and confirmation that these studies will be completed, and if the results are not within specification or potentially not within specification at the end of shelf life, retest period, they will be immediately submitted to the competent authority along with a proposed action plan.

6. Comparison of current and proposed primary packaging specifications (if applicable).

Б.I.в.2 Changing the parameters of the specification and (or) acceptance criteria for the primary packaging of the active pharmaceutical substance	Conditions	Required documentation	Type of procedure
а) tightening specification acceptance criteria	1, 2, 3, 4	1, 2	IA
б) adding a new parameter to the specification and the corresponding test method	1, 2, 5	1, 2, 3, 4, 6	IA
в) exclusion of a non-essential specification parameter (for example, exclusion of an outdated parameter)	1, 2	1, 2, 5	IA
г) adding or replacing a specification parameter for safety or quality reasons		1, 2, 3, 4, 6	IB

Conditions

1. The change is not a consequence of any obligation made as a result of previous examinations to analyze the acceptance criteria for the specification (for example, during registration of a drug or introduction of changes of II type), unless it was previously considered and approved as a follow-up measure.

2. The change is not a consequence of unforeseen situations that have arisen during the production of packaging material or during storage of the active pharmaceutical substance.

3. Any change must be within the range of current approved acceptance criteria.

4. Analytical methodology does not change or changes slightly.

5. No new test method is based on a new non-standard methodology or a standard methodology used in a new way.			
Documentation 1. A change to the relevant section (s) of the dossier. 2. Comparison table of current and proposed specifications. 3. Detailed description of any new analytical method and validation data (when appropriate). 4. Analysis data of two series of packaging material for all specification parameters. 5. Rationale/risk assessment by the HRC or the holder of MFAPS, respectively, confirming that the intra-production parameter is insignificant or outdated. 6. Rationale by the HRC or the holder of MFAPS, respectively, on the new specification parameters and acceptance criteria.			
Б.I.в.3 Changing the analytical methodology for testing the primary packaging of the active pharmaceutical substance	Conditions	Required documentation	Type of procedure
а) minor changes to the approved analytical method	1, 2, 3	1, 2	IA
б) other changes to the analytical method (including additions or replacement)	1, 3, 4	1, 2	IA
в) exclusion of an analytical method if an alternative method has already been approved	5	1	IA
Conditions 1. According to the relevant documents of the Republic of Kazakhstan, the necessary validation was carried out, confirming that the updated analytical method is at least equivalent to the previous one. 2. The analysis method has not changed (for example, changing the column length or temperature, but not a different type of column or method). 3. No new test method is based on new non-standard methods or standard methods used in a new way. 4. The active pharmaceutical substance/drug is not biological/immunological. 5. An analytical method is retained for a specification parameter, and no such method has been added via IA notification.			
Documentation 1. A change to the relevant section (s) of the dossier, including a description of the analytical methodology, a summary of the validation data. 2. Comparative validation results or, if justified, comparative analysis results confirming that the current and proposed tests are equivalent. This requirement does not apply if a new analytical method is added.			

Б.I. г) stability

Б.I.г.1 Changing the retest period, storage period or storage conditions of the active pharmaceutical substance, if the registration dossier does not contain a certificate of	Conditions		Type of procedure

conformity of the European Pharmacopoeia covering the retest period		Required documentation	
a) retest period/storage period 1. Reduction	1	1, 2, 3	IA
2. Increasing the retest period by extrapolating stability data that does not correspond to the documents of the Republic of Kazakhstan (*)			II
3. An increase in the storage period of a biological/immunological active pharmaceutical substance that does not comply with an approved stability study program			II
4. Increase or introduction of a retest period/storage period confirmed by natural storage data		1, 2, 3	IB
б) storage conditions			
1. Changing the storage conditions of the active pharmaceutical substance to more stringent ones	1	1, 2, 3	IA
2. Changing the storage conditions of biological / immunological active pharmaceutical substances, if stability studies were not carried out in accordance with the current approved stability protocol			II
3. Changing the storage conditions of the active pharmaceutical substance		1, 2, 3	IB
в) change of the approved stability study program	1, 2	1, 4	IA
Conditions 1. Changes are not the result of unforeseen situations that have arisen during production, or changes in stability. 2. Changes do not lead to an expansion of the acceptance criteria for the test parameters, the exclusion of the stability parameter, or a decrease in the frequency of tests.			
Documentation 1. A change to the relevant section (s) of the dossier. It is necessary to provide the results of relevant real-time stability studies conducted in accordance with the relevant stability guidelines on at least two (for biological drugs - three) experimental or industrial series of the active pharmaceutical substance, packaged using a registered packaging material, and covering the entire proposed retest period, or the proposed storage conditions.			

2. Confirmation that stability studies have been carried out in accordance with the current approved program. The results of the study should confirm that the relevant approved specifications continue to be met. 3. Copies of approved specifications for the active pharmaceutical substance. 4. Rationale of the proposed changes.	
(*) Note	retest period not applicable to biological/immunological active pharmaceutical substances

Б.I. д) design field and protocol of post-registration changes

Б.I.д.1 Introduction of a new design field or expansion of the approved design field of an active pharmaceutical substance, affecting	Conditions	Required documentation	Type of procedure
a) one operational unit of the manufacturing process of an active pharmaceutical substance, including relevant intra-production controls and (or) analytical methods		1, 2, 3	II
б) analytical methods of source materials / intermediate products and (or) active pharmaceutical substance		1, 2, 3	II
Documentation 1. The design field has been developed based on relevant established requirements and international scientific guidelines. Results of product, process, and analytical methodology studies (e.g., the interaction of various parameters that form the design field to be studied, including risk assessment and multivariate studies, respectively), confirming, as appropriate, that a holistic mechanistic understanding of material quality performance and process parameters at critical quality indicators of the active pharmaceutical substance is achieved. 2. Description of the design field in tabular form, including variables (material properties and manufacturing process parameters) and their proposed ranges. 3. A change to the relevant section (s) of the dossier.			
Б.I.д.2 Introduction of a post-registration protocol for the management of changes affecting the active pharmaceutical substance	Conditions	Required documentation	Type of procedure
		1, 2, 3	II
Documentation 1. A detailed description of the proposed change. 2. Protocol for the management of changes affecting the active pharmaceutical substance. 3. A change to the relevant section (s) of the dossier.			
Б.I.д.3 Exclusion of the post-registration protocol for the management of changes affecting the	Conditions		Type of procedure

active pharmaceutical substance		Required documentation	
	1	1, 2	IA
Conditions 1. Exclusion of the post-registration protocol for the management of changes affecting the active pharmaceutical substance is not a consequence of unforeseen situations or non-compliance with the specification during the introduction of the changes described in the protocol, and does not affect the approved information included in the registration dossier.			
Documentation 1. Rationale for the proposed exclusion. 2. A change to the relevant section (s) of the dossier.			
Б.I.д.4 Changes to the approved change management protocol	Conditions	Required documentation	Type of procedure
а) significant changes to the change management protocol			II
б) minor changes to the change management protocol that do not change the strategy described in the protocol		1	IB
Documentation 1. A declaration that any change must fall within the range of current approved acceptance criteria. In addition, a declaration that a comparability assessment is not required for biological/immunological medicinal products.			
Б.I.д.5 Implementation of changes provided for by the approved change management protocol	Conditions	Required documentation	Type of procedure
а) implementation of the change does not require additional auxiliary data	1	1, 2, 4	IA
б) implementation of the change requires additional auxiliary data		1, 2, 3, 4	IB
в) implementation of the change in a biological/ immunological medicinal product		1, 2, 3, 4, 5	IB
Conditions 1. The proposed change was implemented in full compliance with the approved change management protocol.			
Documentation 1. Link to the approved change management protocol. 2. Declaration that the change complies with the approved change management protocol and that the study results meet the acceptance criteria specified in the protocol. In addition, a declaration that a comparability assessment is not required for biological/immunological medicinal products. 3. Results of studies conducted in accordance with an approved change management protocol. 4. A change to the relevant section (s) of the dossier. 5. A copy of the approved specifications for the active pharmaceutical substance.			

Б.II Medicinal product

Б.II. a) appearance and composition

Б.II.a.1 Changing or adding imprints, engravings or other marks, including replacing or adding ink used in the manufacture of a medicinal product	Conditions	Required documentation	Type of procedure
а) changes in imprints, engravings or other marks	1, 2, 3, 4	1, 2	IB
б) change in breaking lines / scored lines intended for division into equal doses		1, 2, 3	IB
Conditions 1. The specifications of the medicinal product for release and at the end of the shelf-life do not change (except for the appearance). 2. All inks must comply with current pharmaceutical legislation. 3. Notches/fault lines are not intended to be divided into equal doses. 4. Drug symbols used to distinguish dosages have not been completely removed. 3. Breaking lines / scored lines are not intended for division into equal doses. 4. Drug symbols used to distinguish between dosages have not been completely removed.			
Documentation 1. The change to the corresponding section (s) of the dossier, including a detailed graphic or narrative description of the current and new appearance, as well as the corresponding revision of information about the drug. 2. In appropriate cases, samples of the drug. 3. The results of the relevant tests on the State Pharmacopoeia of the Republic of Kazakhstan, confirming the equivalence of properties/correctness of dosage.			
Б.II.a.2 Changing the shape or size of the dosage form	Conditions	Required documentation	Type of procedure
а) tablets, capsules, suppositories and pessaries with immediate release	1, 2, 3, 4	1, 4	IA
б) dosage forms with a delayed, modified or prolonged release and tablets with a breaking line designed to divide into equal doses		1, 2, 3, 4, 5	IB
в) adding a new set for a radiopharmaceutical drug with a different volume of filling			II
Conditions 1. The dissolution profile of the altered drug is comparable to the old one, if applicable. If it is impossible to test the dissolution, the disintegration time of the new drug in comparison with the unchanged one. 2. The specifications of the drug for the release and at the end of the expiration date have not changed (with the exception of the size of the dosage form).			

3. The qualitative and quantitative composition and the average mass have not changed. 4. The change does not affect the tablets with a breaking line designed to divide the dosage form into equal doses.			
Documentation 1. A change to the relevant section (s) of the dossier, including a detailed graphical display of the current and proposed position, as well as revision of information about the medicinal product, respectively. 2. Comparative dissolution data of at least one experimental series with current and proposed sizes (no significant differences in terms of comparability - see the Rules for conducting of bioequivalence studies of medicinal products (hereinafter referred to as the Rules for conducting of bioequivalence studies). For herbal medicinal products, comparative disintegration data are acceptable. 3. Rationale for non-submission of the results of a new bioequivalence study in accordance with the Rules for conducting of bioequivalence studies. 4. Where applicable, samples of the medicinal product. 5. The results of the relevant tests according to the State Pharmacopoeia of the Republic of Kazakhstan, confirming the equivalence of properties / correctness of dosing.			
(*) Note	For Б.II.a.2 в), any change in the “dosage” of a medicinal product requires an application for an extension of registration		
Б.II.a.3 Changing the composition (excipients) of the medicinal product	Conditions	Required documentation	Type of procedure
a) change in the composition of flavors (flavors) or dyes			
1. Addition, exclusion or replacement	1, 2, 3, 4, 5, 6, 7, 9	1, 2, 4, 5, 6	IB
2. Increase or decrease of content	1, 2, 3, 4	1, 2, 4	IB
б) other excipients			
1. Any minor correction of the quantitative composition of the excipients of the medicinal product	1, 2, 4, 8, 9, 10	1, 2, 7	IB
2. Qualitative or quantitative changes in one or more excipients that significantly affect the quality, safety or efficacy of the medicinal product			II
3. Change affecting the biological/immunological product			II
4. Any new excipient involving materials of human or animal origin requiring evaluation of viral safety data and/or TSE risk			II
5. Change justified by the results of the bioequivalence study			II

6. Replacement of one excipient with a similar excipient with the same functional characteristics in the same amount		1, 3, 4, 5, 6, 7, 8, 9	IB

Conditions

1. There are no changes in the functional characteristics of the dosage form, for example, fragmentation time, dissolution profile.

2. Any minor correction of the composition to maintain the total mass must be carried out with the excipient, which currently constitutes the main part of the medicinal product.

3. The specification of the medicinal product has been updated in terms of appearance/smell/taste and, if necessary, the identity test has been eliminated.

4. Appropriate stability studies have been started in accordance with the established requirements (indicating numbers of series); the relevant stability parameters were analyzed for at least two experimental or industrial series; the applicant has satisfactory results of at least a three-month stability study (at the time of the introduction of type IA changes and notification of type IB changes); the stability profile is similar to the currently approved profile. Confirmation that the studies will be completed, and that if the results at the end of the expiration date are not within specification or potentially not within specification, they will be immediately submitted to the competent authority along with a proposed action plan. In addition, photostability testing should be carried out where appropriate.

5. All new components must meet the requirements of the relevant documents of the Republic of Kazakhstan regarding dyes used in the food industry and flavoring additives.

6. No new component involves the use of materials of human or animal origin that require evaluation of viral safety data or compliance with the current requirements of the State Pharmacopoeia of the Republic of Kazakhstan to minimize the risk of transmission of agents of animal spongiform encephalopathy through medicinal products for medical and veterinary use.

7. Where appropriate, changes do not affect differences between dosages and do not adversely affect the taste properties of medicinal products intended for children.

8. The dissolution profile of at least two experimental series of a new medicinal product is comparable to the unchanged one (no significant differences in terms of comparability - see the Rules for conducting of bioequivalence studies). If it is not possible to conduct a dissolution test with herbal medicinal products, the fragmentation time of a new medicinal product is comparable to that of the unchanged one.

9. The change is not the consequence of instability and (or) should not affect safety, that is, differences between dosages.

10. The considered medicinal product is not a biological/immunological medicinal product.

Documentation

1. A change to the relevant section (s) of the dossier, including methods for testing the authenticity of all new dyes (if applicable), as well as revision of information on the medicinal product, respectively.

2. Declaration that the required stability studies have been started in accordance with the established requirements (indicating numbers of series); and that (if applicable) the required minimum satisfactory stability data were available at the time of the change; available data did not indicate any problem. Confirmation must also be provided that the studies will be completed and that if the results are not within specification or potentially not within specification at the end of the expiration date, they will be immediately submitted to the competent authority along with a proposed action plan.

3. Results of stability studies carried out in accordance with the established requirements for significant stability parameters on at least two experimental or industrial series covering at least 3 months, and confirmation that these studies will be completed, and if the results are not within specification or potentially not within specification at the end of the expiration date, they will be immediately submitted to the competent authority along with a proposed action plan.

4. Where applicable, samples of the new medicinal product.

5. Either a certificate of compliance with the European Pharmacopoeia for TSE for any new source of material, or (if applicable) documentary confirmation that the source of material at risk of TSE has previously been verified

by an authorized body; and its compliance with the current article of the State Pharmacopoeia of the Republic of Kazakhstan on minimizing the risk of transmission of agents of animal spongiform encephalopathy through medicinal products for medical and veterinary use was confirmed. For each such material, the following information must be provided: the name of the manufacturer; type of animal and tissue from which the material is obtained; country of origin of animals and its use.

6. Where appropriate, evidence that the new excipient does not interact with the analytical procedures for drug product specification.

7. Justify the change/selection of excipients, etc. through sound pharmaceutical development (including stability and antimicrobial preservation, if applicable).

8. Comparative data on the dissolution profile of solid dosage forms on at least two experimental series of a medicinal product of new and old compositions. For herbal medicinal products, comparative fragmentation data are sufficient.

9. Rationale for non-submission of the results of a new bioequivalence study in accordance with the Rules for conducting of bioequivalence studies.

Б.II.a.4 Change in the mass of the shell of oral dosage forms or change in the mass of the capsule shell	Conditions	Required documentation	Type of procedure
а) solid dosage forms for oral administration	1, 2, 3, 4	1, 2	IB
б) delayed, modified or extended release dosage forms in which the shell is a key release factor			II

Conditions

1. The dissolution profile of at least two experimental series of a new medicinal product is comparable to the old one. If it is not possible to conduct a dissolution test with herbal medicinal products, the fragmentation time of a new medicinal product in comparison with the old one.

2. The shell is not a key factor in the release mechanism.

3. The specification of the medicinal product has been updated only in terms of mass and sizes (if applicable).

4. Appropriate stability studies have been started in accordance with the established requirements on at least two experimental or industrial series; the applicant has satisfactory data at the time of the introduction of the changes, at least three months stability data; confirmation that the studies will be completed. If the results are not within the specification, or potentially may not be within the specification at the end of the expiration date, they will be immediately submitted to the competent authority along with a proposed action plan.

Documentation

1. A change to the relevant section (s) of the dossier.

2. Declaration that the required stability studies have been started in accordance with the established requirements (indicating numbers of series); and that (if applicable) the required minimum satisfactory stability data were available at the time of the change; available data did not indicate any problem. Confirmation must also be provided that the studies will be completed and that if the results are not within specification or potentially not within specification at the end of the expiration date, they will be immediately submitted to the competent authority along with a proposed action plan. In addition, photostability testing should be carried out where appropriate.

Б.II.a.5 Change in the concentration of a single-dose, fully administered parenteral medicinal product with the	Conditions		Type of procedure

same content of active pharmaceutical substance per dose unit (i.e. dosage)		Required documentation	
			II
Б.II.a.6 Removing the solvent/diluent container from packaging	Conditions	Required documentation	Type of procedure
		1, 2	IB
Documentation 1. Rationale for the exclusion, including an indication of alternative ways to obtain a solvent / diluent for safe and effective use of the medicinal product. 2. Revised medicinal product information.			

Б.II. б) Production

B.II.b.1 Replacement or addition of manufacturing site for part or all of drug product manufacturing processes	Conditions	Required documentation	Procedure type
a) secondary packaging area	1, 2	1, 3, 8	IA
b) primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IA
c) primary packaging site d) a site where production operations shall be carried out for biological, immunological drugs or dosage forms produced by complex production processes, with the exception of batch release, batch quality control and secondary packaging			II
e) a site requiring a primary inspection or a product of a specific inspection			II
f) site where any manufacturing operations for non-sterile medicinal products shall be carried out, with the exception of batch release, batch control , primary and secondary packaging		1, 2, 3, 4, 5, 6, 7, 8, 9	IB
g) a site where any production operations shall be carried out with sterile drugs manufactured using aseptic methods (excluding biological, immunological			IB

drugs), with the exception of batch release, batch quality control and secondary packaging		1, 2, 3, 4, 5, 7, 8	

Conditions

1. Availability of the Certificate of Good Manufacturing Practice (GMP) of the manufacturing site of the transmitting and receiving parties.

2. The site shall be licensed in accordance with the established procedure (for the production of the considered dosage form or medicinal product).

3. The drug product in question shall not be sterile.

4. Where appropriate, for example for suspensions or emulsions, there is a validation scheme or a new site with at least three commercial batches has been successfully validated in accordance with the current protocol.

5. The drug product in question shall not be biological/immunological.

Documentation

1. Availability of the Certificate of Good Manufacturing Practice (GMP) of the manufacturing site of the transmitting and receiving parties.

2. Where applicable, the batch numbers, the corresponding batch size and the manufacturing date of the batches (3) used in the validation study shall be indicated and the validation data or validation protocol (scheme) to be submitted is provided.

3. The "current" and "proposed" manufacturers of the medicinal product (according to section 2.5 of the application form) are clearly indicated in the form of the application for amendments.

4. Copies of approved release and end of shelf-life specifications (if applicable).

5. Analysis data of one production batch and two pilot production batches simulating the manufacturing process (or two production batches) and comparative data with three batches produced at the previous production site. Data for the following two complete industrial batches shall be provided upon request; shall be reported if the results of the analysis do not fit into the specification and an action plan is proposed.

6. Relevant validation data including microscopy of particle size distribution and morphology of soft and liquid dosage forms in which the drug substance is undissolved.

7. If the drug substance is used as the starting material at the new production site, the declaration of the authorized person of the site responsible for the release of batches that the drug substance is produced in accordance with the Rules of Good Manufacturing Practice of the Republic of Kazakhstan for the starting materials shall be used.

8. Amendment to the relevant section (s) of the dossier.

9. If the manufacturing site and the primary packaging site are different, (bulk) transportation and storage conditions are described and validated.

Notes:	When introducing amendments to the manufacturing site in the country and outside the Republic of Kazakhstan, with which the agreement on mutual recognition of GMP has not been concluded, the marketing authorization holders shall be advised to consult with the authorized body and submit information about all previous inspections for the last 2-3 years and (or) all scheduled inspections, including inspection dates, categories of inspected products, supervisory authority and other information. Declarations of the authorized person affecting the active substance. Manufacturing license holders shall use only GMP-manufactured active pharmaceutical substances as starting materials, so each manufacturing license holder declares that they use GMP-manufactured active pharmaceutical substance as starting material. In addition, since the qualified person responsible for batch certification is responsible for each batch, if the batch site differs from the above, the authorized person responsible for batch certification shall submit an additional declaration. If there is one production license holder, only one declaration is provided. If multiple manufacturing license holders are involved, instead of filing multiple declarations,

	one declaration signed by one authorized person is submitted, provided the declaration clearly states that it is signed on behalf of all authorized persons involved .		
Б.II.б.2 Change of importer , series release agreements and drug quality control testing	Conditions	Required documentation	Type of procedure
а) replacement or addition of a site for quality control/ series testing	1, 2, 3	1, 2	IA
б) replacement or addition of a manufacturer responsible for the release of series of a biological/ immunological medicinal product and any test methods carried out on the site that are a biological/ immunological method			II
в) replacement or addition of a manufacturer responsible for the release of series			
1. Except for quality control/ series testing	1	1, 2, 3, 4	IA
2. Including quality control /series testing	1, 2, 3,	1, 2, 3, 4	IA
3. Including quality control /biological/immunological medicinal product testing and one of the on-site testing methods is biological/immunological/ immunochemical			II
Conditions 1. The site is licensed in the prescribed manner. 2. The medicinal product is not a biological/immunological medicinal product. 3. The transfer of technology from the old to the new site or new testing laboratory was successful.			
Documentation 1. A copy of production licenses or, in their absence, a GMP certificate issued within the last three years by the relevant authorized body. 2. In the application form for changes, it is necessary to indicate the “current” and “proposed” manufacturers of the medicinal product (according to section 2.5 of the application form). 3. Declaration of the authorized person responsible for certification of the series, which indicates that the manufacturer (s) of the active pharmaceutical substance specified in the registration dossier work (s) in accordance with the Rules of Good Manufacturing Practice of the Republic of Kazakhstan for source materials. Under certain circumstances, it is allowed to submit one declaration (see note to the change Б.II.б.1). 4. A change to the relevant section (s) of the dossier, including information about the medicinal product.			
Б.II.б.3 Changing the manufacturing process of a medicinal product,			

including an intermediate product used in the manufacture of a medicinal product	Conditions	Required documentation	Type of procedure
а) minor changes in the production process	1, 2, 3, 4, 5, 6, 7	1, 3, 4, 5, 6, 7, 8	IB
б) significant changes in the manufacturing process that have a significant impact on the quality, safety and efficacy of the medicinal product			II
в) medicinal product is biological/immunological and the change requires an assessment of comparability			II
г) introduction of a non-standard terminal sterilization method			II
д) introduction or increase of the excess used in relation to the active pharmaceutical substance			II
е) minor change in the production process of an aqueous suspension for oral administration		1, 2, 4, 6, 7, 8	IB
Conditions 1. There are no changes in the qualitative or quantitative profile of impurities or physico-chemical properties. 2. The change relates to a solid oral dosage form (oral solution) with immediate release and the medicinal product in question is not a biological / immunological or herbal. 3. The principle of production, including its individual stages, does not change, for example, the processing of intermediate products, there are no changes in any solvents used in the production process. 4. The currently registered production process is controlled by internal production controls and changes in such controls (expansion or elimination of acceptance criteria) are not required. 5. The specifications of the medicinal product or intermediates do not change. 6. Based on the results of the new process, a medicinal product identical in terms of all aspects of quality, safety and efficacy should be formed. 7. According to the relevant documents of the Republic of Kazakhstan, relevant stability studies have been started on at least one experimental or industrial series; the applicant has at his disposal satisfactory results of at least a three-month stability study. Confirmation that studies will be completed and if the results are not within specification or potentially not within specification at the end of the expiration date, they will be immediately submitted to the competent authority along with a proposed action plan.			
Documentation 1. A change to the relevant section (s) of the dossier. 2. For soft and liquid dosage forms in which the active pharmaceutical substance is in an undissolved state: proper validation of the change, including particle microscopy in order to check for visible changes in morphology; comparative data on the distribution of particle size (dispersion), obtained in an appropriate way. 3. For solid dosage forms: dissolution profile data from one representative industrial series and comparative data from the last three series produced by the previous process. Upon request, provide data for the next two complete			

industrial series or report if the results do not fit into the specification and propose a plan of action. For herbal medicinal products, comparative fragmentation data are sufficient.

4. Rationale for non-submission of the results of a new bioequivalence study in accordance with the Rules for conducting of bioequivalence studies.

5. When changing the parameter (s) of the process, which are considered not to affect the quality of the medicinal product, a declaration that this was achieved in the course of a previously approved risk assessment.

6. Copies of specifications for release and at the end of the expiration date.

7. Series analysis data (in comparative table format) from at least one series produced by an approved and proposed process. Upon request, data for the following two complete industrial series must be provided; should report if the results of the analysis do not fit into the specification and propose an action plan.

8. Declaration that the relevant stability studies have been started in accordance with the documents of the Republic of Kazakhstan (indicating numbers of series) and the necessary stability parameters have been studied on at least one experimental or industrial series and at the time of notification the applicant had satisfactory results, at least a three-month stability study; and the stability profile is similar to the current registered situation. Confirmation is provided that the studies will be completed and that if the results are not within specification, or potentially not within specification at the end of the expiration date, they will be submitted immediately to the competent authority along with a proposed action plan.

Б.II.б.4 Changing the series size (including series size ranges) of a medicinal product	Conditions	Required documentation	Type of procedure
а) enlargement up to 10 times compared to the approved	1, 2, 3, 4, 5, 7	1, 4	IB
б) downscaling up to 10 times	1, 2, 3, 4, 5, 6	1, 4	IB
в) the change requires a comparability analysis of the biological/ immunological medicinal product or a change in the series size requires a new bioequivalence study			II
г) the change affects all other dosage forms produced using complex manufacturing processes			II
д) enlargement more than 10 times compared to the approved size of the series of dosage forms with immediate release (for oral administration)		1, 2, 3, 4, 5, 6	IB
е) the scale of production of a biological / immunological medicinal product has increased / decreased without changing the production process (for example, duplication of the line)		1, 2, 3, 4, 5, 6	IB

Conditions 1. The change does not affect the reproducibility and (or) constancy of the quality of the medicinal product. 2. The change affects immediate-release oral dosage forms or non-sterile liquid dosage forms. 3. Any changes to production methods and/or intra-production controls are only necessary to change the series size, such as using a different size of equipment. 4. A validation scheme is in place or, in accordance with the current protocol, production has been successfully validated on at least three industrial series with a new size in accordance with applicable requirements. 5. The medicinal product in question is not a biological/immunological one. 6. The change should not be the result of unforeseen situations that arose during production, or a change in stability. 7. The series size is within 10 times the range provided at registration or after a subsequent change that was not a type IA change.			
Documentation 1. A change to the relevant section (s) of the dossier. 2. Series analysis data (in comparative table format), three industrial series produced in registered and offered sizes. The HRC is obliged to report if the results of the analysis do not fit into the specification and propose an action plan. 3. Copies of approved specifications for release and at the end of the expiration date. 4. Where applicable, numbers of series corresponding to the series size and production date (3) used in the validation study should be provided, or a validation report (result) of the manufacturing process for the claimed series size should be submitted. 5. It is necessary to present the results of the validation. 6. The results of stability studies carried out in accordance with the documents of the Republic of Kazakhstan, on significant stability parameters, under accelerated and long-term test conditions on three experimental or industrial series covering at least three months; confirmation that such studies will be completed and that if the results are not within specification or potentially not within specification at the end of the expiration date, they will be immediately submitted to the competent authority along with a proposed action plan. For biological/ immunological agents: a declaration that a comparability assessment is not required.			
Б.II.б.5 Changing intra-production tests or acceptance criteria used in the manufacture of a medicinal product	Conditions	Required documentation	Type of procedure
а) tightening intra-production acceptance criteria	1, 2, 3, 4	1, 2	IA
б) adding new tests or acceptance criteria	1, 2, 5, 6	1, 2, 3, 4, 5, 7	IB
в) exclusion of a non-essential intra-production test	1, 2, 7	1, 2, 6	IA
г) exclusion of intra-production testing, which can significantly affect the overall quality of the medicinal product			II
д) expansion of approved intra-production acceptance criteria that			II

significantly affect the overall quality of the medicinal product			
e) addition or replacement of intra-production testing for safety or quality reasons		1, 2, 3, 4, 5, 7	IB
Conditions 1. The change is not a consequence of any obligation made as a result of previous examinations in order to analyze the acceptance criteria for the specification (for example, during registration or introduction of type II changes). 2. The change is not a consequence of unforeseen situations that arose during production, for example, a new unqualified impurity, a change in the limits for the content of the amount of impurities. 3. Any change must be within the range of currently approved acceptance criteria. 4. Analytical procedure does not change or changes slightly. 5. No new test method is based on a new non-standard methodology or a standard methodology used in a new way. 6. The new test method is not a biological/immunological/immunochemical method or a method that uses a biological reagent for a biologically active pharmaceutical substance (with the exception of standard pharmacopoeial microbiological methods). 7. Intra-production testing does not affect the control of a critical parameter, for example: impurity quantification (unless a specific solvent is clearly used in production), any critical physical characteristic (particle size, bulk density before and after compaction, etc.), test for identity (in the absence of a suitable alternative control), microbiological control (unless required for a particular dosage form).			
Documentation 1. A change to the relevant section (s) of the dossier. 2. Comparison table of current and proposed int5ra-production tests and acceptance criteria. 3. Detailed description of the new analytical method and validation data (if applicable). 4. Data from the analysis of two industrial series (in the absence of proper rationale for biologically active pharmaceutical substances - three series) of the medicinal product for all specification parameters. 5. Where applicable, comparative dissolution profile data of the medicinal product on at least one experimental series produced using current and new int5ra-production tests. For herbal medicinal products, there may be residual comparative fragmentation data. 6. Rationale/risk assessment confirming that the intra-production test is irrelevant or outdated. 7. Rationale for the new intra-production test and acceptance criteria.			

Б.II. в) quality control of excipients

Б.II.в.1 Changing specification parameters and (or) excipient acceptance criteria	Conditions	Required documentation	Type of procedure
а) tightening specification acceptance criteria	1, 2, 3, 4	1, 2	IA
б) adding a new specification parameter and corresponding test method to the specification	1, 2, 5, 6, 7	1, 2, 3, 4, 6, 8	IB
в) exclusion of a non-essential specification	1, 2		IA

parameter (for example, exclusion of an outdated parameter)		1, 2, 7	
г) a change outside the approved specification acceptance criteria			II
д) exclusion of a specification parameter that can significantly affect the overall quality of the medicinal product			II
е) addition or substitution (excluding biological and immunological product) of a specification parameter and corresponding test method for reasons of safety or quality		1, 2, 3, 4, 5, 6, 8	IB
ж) if there is no article of the State Pharmacopoeia of the Republic of Kazakhstan for the excipient, a change in the own specification data for an unofficial pharmacopoeia or a pharmacopoeia of a third country		1, 2, 3, 4, 5, 6, 8	IB
Conditions 1. The change is not a consequence of any obligation taken as a result of previous examinations in order to analyze the acceptance criteria for the specification (for example, during registration of a medicinal product or introduction of type II changes). 2. The change is not a consequence of unforeseen situations that arose during production, for example, a new unqualified impurity, a change in the limits for the content of the amount of impurities. 3. Any change must be within the range of current approved acceptance criteria. 4. Analytical procedure does not change or changes slightly. 5. No new test method is based on a new non-standard methodology or a standard methodology used in a new way. 6. The new test method is not a biological/immunological/immunochemical method or a method that uses a biological reagent for a biologically active pharmaceutical substance (with the exception of standard pharmacopoeial microbiological methods). 7. The change does not apply to the genotoxic impurity.			
Documentation 1. A change to the relevant section (s) of the dossier. 2. Comparative table of current and proposed specifications. 3. Detailed description of any new analytical method and validation data (if applicable). 4. Data from the analysis of two industrial series (in the absence of proper rationale for biologically active pharmaceutical substances - three series) of the excipient for all specification parameters. 5. Where appropriate, test data for comparative drug dissolution kinetics of at least one experimental series containing an excipient that complies with current and proposed specifications. For herbal medicinal products, comparative fragmentation data are sufficient.			

6. Rationale for non-submission of the results of a new bioequivalence study in accordance with the Rules for conducting of bioequivalence studies.
7. Rationale /risk assessment confirming that the parameter is insignificant or obsolete.
8. Rationale for the new specification parameter and acceptance criteria.

Б.II.в.2 Changing of analytical procedure for excipient	Conditions	Required documentation	Type of procedure
а) minor changes to an approved analytical method	1, 2, 3, 4	1, 2	IA
б) exclusion of an analytical method if an alternative method has already been approved	5	1	IA
в) replacement of a biological/immunological/ immunochemical test method or a method that uses a biological reagent			II
г) other changes to the analytical method (including additions or replacement)		1, 2	IB

Conditions
1. According to the relevant documents, the necessary validation studies have been carried out, confirming that the updated analytical method is at least equivalent to the previous one.
2. The limits of the content of the amount of impurities have not changed, new unqualified impurities have not been detected.
3. The method of analysis has not changed (for example, changing the column length or temperature, but not a different type of column or method).
4. The new test method is not a biological/immunological/immunochemical method or a method that uses a biological reagent (with the exception of standard pharmacopoeial microbiological methods).
5. An alternative analytical method for the specification parameter has already been approved, at that the method was included not via the IA/-notification.

Documentation
1. A change to the relevant section (s) of the dossier, including a description of the analytical methodology, a summary of the validation data, revised specifications for impurities (if applicable).
2. Comparative validation results or, if justified, comparative analysis results demonstrating that the current and proposed tests are equivalent. This requirement does not apply if a new analytical method is added.

Б.II.в.3 Changing the source of obtaining an excipient or reagent with a risk of TSE	Conditions	Required documentation	Type of procedure
а) from a material with a TSE risk to a material of plant or synthetic origin			
1. For excipients or reagents not used in the production of a biological/ immunological active pharmaceutical substance	1		IA

or a biological/ immunological medicinal product		1	
2. For excipients or reagents used in the manufacture of a biological /immunological active pharmaceutical substance or a biological/ immunological medicinal product		1, 2	IB
б) a change or introduction of a material with a TSE risk or replacement of a material with a TSE risk with another material with a TSE risk that does not have a TSE certificate of conformity			II
Conditions 1. Specifications for the release and at the end of the expiration date of the excipient and the medicinal product do not change.			
Documentation 1. Declaration by the manufacturer or the HRC of the material that they are entirely of plant or synthetic origin. 2. Study of the equivalence of materials and the impact on the production of the finished material, and the impact on the characteristics (eg, dissolution characteristics) of the medicinal product.			
Б.II.в.4 Change in the synthesis or preparation of a non-pharmacopoeial excipient (if described in the registration dossier) or a new excipient	Conditions	Required documentation	Type of procedure
а) minor change in the synthesis or preparation of a non-pharmacopoeial excipient or a new excipient	1, 2	1, 2, 3, 4	IB
б) specifications are changed or there is a change in the physicochemical properties of the excipient that affect the quality of the medicinal product			II
в) excipient biological / immunological substance			II
Conditions			

1. The synthesis method and specifications are identical and there are no qualitative and quantitative changes in the impurity profile (excluding residual solvents, provided that their control is carried out in accordance with the limit content specified in the documents of the Republic of Kazakhstan) or physico-chemical properties. 2. Adjuvants are excluded.
Documentation 1. A change to the relevant section (s) of the dossier. 2. Series analysis data (in comparative table format) of at least two series (at least experimental ones) of the excipient produced by the old and new processes. 3. Where appropriate, comparative drug dissolution kinetics test data from at least two series (at least experimental ones). For herbal medicinal products, comparative fragmentation data are sufficient. 4. A copy of the approved and new (if applicable) specifications for the excipient.

Б.II. г) drug quality control

Б.II.г. 1 Changing specification parameters and (or) acceptance criteria for a medicinal product	Conditions	Required documentation	Type of procedure
а) tightening specification acceptance criteria	1, 2, 3, 4	1, 2	IB
б) tightening of specification acceptance criteria of medicinal products subject to series release by an official control body	1, 2, 3, 4	1, 2	IB
в) adding a new parameter and the corresponding test method to the specification	1, 2, 5, 6, 7	1, 2, 3, 4, 5, 7	IB
г) exclusion of a non-essential specification parameter (for example, exclusion of an outdated parameter)	1, 2	1, 2, 6	IA
д) a change outside the approved specification acceptance criteria			II
е) exclusion of a specification parameter that can significantly affect the total quality of the medicinal product			II
ж) addition or substitution (excluding biological and immunological preparations) of a specification parameter and its corresponding test method for reasons of safety or quality		1, 2, 3, 4, 5, 7	IB
з) updating the dossier in order to comply with the			

provisions of the updated general article of the State Pharmacopoeia of the Republic of Kazakhstan for the medicinal product (*)	1, 2, 3, 4, 7, 8	1, 2	IA
и) an article of the State Pharmacopoeia of the Republic of Kazakhstan " Uniformity of dosing" is introduced in order to replace the current registered method, or an article of the State Pharmacopoeia of the Republic of Kazakhstan " Uniformity of mass", or " Uniformity of contents"	1, 2, 10	1, 2, 4	IA
Conditions 1. The change is not a consequence of any obligation made as a result of previous expertise to revise the acceptance criteria for a specification (for example, during registration of a medicinal product or introduction of type II changes), unless the supporting documentation has been previously reviewed and approved within the framework of another procedure. 2. The change is not a consequence of unforeseen situations that arose during production, for example, of a new unqualified impurity, a change in the limits for the content of the amount of impurities. 3. Any change must be within the range of current approved acceptance criteria. 4. Analytical procedure does not change or changes slightly. 5. No new test method is based on a new non-standard methodology or a standard methodology used in a new way. 6. The new test method is not a biological/immunological/immunochemical method or a method that uses a biological reagent for a biologically active pharmaceutical substance (with the exception of standard pharmacopoeial microbiological methods). 7. The change does not affect any impurities (including genotoxic) or dilution. 8. The change affects the updating of the acceptance criteria for microbiological controls in order to comply with the current Pharmacopoeia, and the currently registered acceptance criteria for microbiological controls do not include any additional controls included in the specification, in addition to the pharmacopoeial requirements for a particular dosage form. 9. The specification parameter does not affect a critical parameter, for example: impurity quantification (unless a certain solvent is clearly used in the manufacture of a medicinal product), any critical physical characteristic (strength or friability of uncoated tablets, dimensions), any request to skip a test . 10. The proposed control fully complies with the table of the article of the State Pharmacopoeia of the Republic of Kazakhstan and does not include alternative proposals for testing the uniformity of dosing by varying the mass or uniformity of the content, if the latter are indicated in the article.			
Documentation 1. A change to the relevant section (s) of the dossier. 2. Comparison table of current and proposed specifications. 3. Detailed description of any new analytical method and validation data (if applicable). 4. Data from the analysis of two industrial series (in the absence of proper justification for biologically active pharmaceutical substances - three series) of the medicinal product for all specification parameters. 5. Where appropriate, comparative drug dissolution kinetics test data from at least one experimental series, in accordance with current and proposed specifications. For herbal medicinal products, comparative fragmentation data are sufficient.			

6. Rationale/risk assessment confirming that the parameter is not significant. 7. Rationale for the new specification parameter and acceptance criteria.			
(*) Note	if the “current edition” is mentioned in the dossier of the registered medicinal product, there is the need to notify the authorized bodies about the updated article of the State Pharmacopoeia of the Republic of Kazakhstan. In this regard, such a change is applied in the absence of a mention of the updated pharmacopoeial article in the technical dossier, and the change is made in order to include a mention of the updated version.		
Б.II.г.2 Changing the analytical method of the medicinal product	Conditions	Required documentation	Type of procedure
а) minor changes to the approved analytical method	1, 2, 3, 4	1, 2	IB
б) exclusion of an analytical method if an alternative method has already been approved	4	1	IA
в) change (replacement) of a biological/immunological /immunochemical test or method in which a biological reagent is used, or replacement of a biological reference product not covered by an approved protocol			II
г) other changes to the analytical method (including additions or replacement)		1, 2	IB
д) updating the analytical methodology in order to comply with the updated general article of the State Pharmacopoeia of the Republic of Kazakhstan	2, 3, 4, 5	1	IA
е) in order to reflect the compliance with the State Pharmacopoeia of the Republic of Kazakhstan and exclude the mention of an outdated own analytical method and its number (*)	2, 3, 4, 5	1	IA
Conditions 1. According to the relevant documents, the necessary validation studies have been carried out, confirming that the updated analytical method is at least equivalent to the previous one. 2. The limits of the content of the amount of impurities have not changed, new unqualified impurities have not been detected. 3. The analysis method has not changed (for example, changing the column length or temperature, but not a different type of column or method).			

4. The new test method is not a biological/immunological/immunochemical method or a method that uses a biological reagent (with the exception of standard pharmacopoeial microbiological methods). 5. The registered analytical method already refers to the general article of the State Pharmacopoeia of the Republic of Kazakhstan, and any changes are insignificant and require updating the technical dossier.			
Documentation 1. A change to the relevant section (s) of the dossier, including a description of the analytical methodology, a summary of the validation data, revised specifications for impurities (if applicable). 2. Comparative validation results or, if justified, comparative analysis results confirming that the current and proposed tests are equivalent. This requirement does not apply if a new analytical method is added.			
(*) Note	if the “current edition” is mentioned in the dossier of the registered medicinal product, there is no need to notify the authorized bodies about the updated article of the State Pharmacopoeia of the Republic of Kazakhstan.		
Б.II.г.3 A change affecting the introduction of real-time release or release by parameters in the manufacture of a medicinal product	Conditions	Required documentation	Type of procedure
			II

Б.II. д) packaging and sealing system

Б.II.д.1 Change in the primary packaging of the medicinal product	Conditions	Required documentation	Type of procedure
а) qualitative and quantitative composition			
1. Solid dosage forms	1, 2, 3	1, 2, 3, 4, 6	IB
2. Soft and non-sterile liquid dosage forms		1, 2, 3, 5, 6	IB
3. Sterile medicinal products and biological/ immunological medicinal products			II
4. The change affects packaging that has less protective properties while changing storage conditions and (or) reducing the shelf life			II
б) changing the type of container or adding a new container			
1. Solid, soft and non-sterile liquid dosage forms		1, 2, 3, 5, 6, 7	IB
2. Sterile medicinal products and biological/ immunological medicinal products			II

3. Exclusion of the primary packaging container that does not lead to the complete elimination of the dosage or dosage form	4	1, 8	IA
Conditions 1. The change only affects the same type of packaging/container (for example, blister to blister). 2. In terms of significant properties, the proposed packaging material is at least equivalent to the approved one. 3. Appropriate stability studies have been started in accordance with the established requirements and the applicant, at the time of the introduction of the changes, has analyzed the relevant stability parameters on at least two experimental or industrial series, he has at his disposal satisfactory results of at least a three-month stability study. However, if the proposed package is more stable than the approved package, then three-month stability data is not required. Studies are terminated if their results are not within the specifications or potentially will not be within the specifications at the end of the expiration date, they must be immediately submitted to the competent authority along with the proposed action plan. 4. The remaining formulation(s) of the medicinal product must be sufficient to fulfill the recommendations for dosage and duration of treatment specified in the general characteristics of the medicinal product.			
Documentation 1. A change to the relevant section (s) of the dossier. 2. Required data for new packaging (e.g. comparative permeability data, e.g. O2, CO2, moisture, etc.). 3. In appropriate cases, it is necessary to provide confirmation that the interaction between the contents and the packaging material does not occur (for example, there is no movement of the components of the proposed material into its contents, the components of the medicinal product do not pass into the package), including confirmation that the material meets the relevant pharmacopoeial requirements or the legislation of the Republic of Kazakhstan on plastic materials and objects in contact with food. 4. Declaration that the required stability studies have been started in accordance with the established requirements (indicating numbers of series); and that (where applicable) the required minimum satisfactory stability data were available to the applicant at the time of the change; the available data did not indicate any problem. Confirmation must also be provided that the studies will be completed and that if the results are not within specification or potentially not within specification at the end of the expiration date, they will be immediately submitted to the competent authority along with a proposed action plan. 5. The results of stability studies conducted in accordance with established requirements, for significant stability parameters on at least two experimental or industrial series covering at least 3 months, and confirmation that these studies will be completed, and if the results are not within specification or potentially not within specification at the end of the expiration date, they will be immediately submitted to the competent authority along with a proposed action plan. 6. Comparison of current and proposed primary packaging specifications (if applicable). 7. If applicable, samples of the new container/sealing. 8. Declaration that the remaining size (s) of the package correspond to the dosing regimen and duration of treatment and is sufficient to fulfill the dosing recommendations given in the general characteristics of the medicinal product.			
Note	For Б.II.Д.1.б) - if the change leads to the "formation of a new dosage form", then such a change requires an application for registration extension		
Б.II.д.2 Changing the parameters of the specification and (or) acceptance criteria for the primary packaging of the medicinal product	Conditions	Required documentation	Type of procedure
a) tightening specification acceptance criteria	1, 2, 3, 4	1, 2	IA

б) adding a new parameter and the corresponding analytical method to the specification	1, 2, 5	1, 2, 3, 4, 6	IB
в) exclusion of a non-essential specification parameter (for example, exclusion of an outdated parameter)	1, 2	1, 2, 5	IA
г) adding or replacing a specification parameter for safety or quality reasons		1, 2, 3, 4, 6	IB
Conditions 1. The change is not a consequence of any obligation taken as a result of previous examinations in order to analyze the acceptance criteria for the specification (for example, during registration of a medicinal product or introduction of type II changes). 2. The change is not the result of unforeseen situations that have arisen in the course of production. 3. Any change must be within the range of current approved acceptance criteria. 4. Analytical procedure does not change or changes slightly. 5. No new test method is based on a new non-standard methodology or a standard methodology used in a new way.			
Documentation 1. A change to the relevant section (s) of the dossier. 2. Comparison table of current and proposed specifications. 3. Detailed description of the new analytical method and validation data (if applicable). 4. Analysis data of two series of packaging material for all parameters (indicators) of the specification. 5. Rationale /risk assessment confirming that the parameter is not significant. 6. Rationale for the new specification parameter and acceptance criteria.			
Б.II.д.3 Changing the analytical method for the primary packaging of the medicinal product	Conditions	Required documentation	Type of procedure
а) minor changes to an approved analytical method	1, 2, 3	1, 2	IB
б) other changes to the analytical method (including replacement or addition)	1, 3, 4	1, 2	IB
в) exclusion of an analytical method if an alternative method has already been approved	5	1	IA
Conditions 1. According to the relevant documents, the necessary validation has been carried out, confirming that the updated analytical method is at least equivalent to the previous one. 2. The method of analysis has not changed (for example, changing column length or temperature, but not another column or method). 3. No new test method is based on a new non-standard methodology or a standard methodology used in a new way. 4. The active pharmaceutical substance/drug is not biological/immunological.			

5. An alternative analytical method for the specification parameter has already been approved, at that the method was included not via the IA/-notification.			
Documentation 1. A change to the relevant section (s) of the dossier. 2. Comparative validation results or, if justified, comparative analysis results confirming that the current and proposed tests are equivalent. This requirement does not apply if a new analytical method is added.			
Б.II.д.4 Changing the shape or dimensions of the primary packaging or sealing (primary packaging)	Conditions	Required documentation	Type of procedure
а) non-sterile drugs	1, 2, 3	1, 2, 4	IB
б) a change in shape or size affects key indicators of the packaging material that significantly affect the delivery, use, safety or stability of the medicinal product			II
в) sterile drugs		1, 2, 3, 4	IB
Conditions 1. The qualitative and quantitative composition of the primary packaging has not changed. 2. The change does not affect the key quality indicators of the packaging material that affect the delivery, use, safety or stability of the medicinal product. 3. When changing the free space or the surface / volume ratio, in accordance with the relevant documents of the Republic of Kazakhstan on stability, appropriate stability studies have been started; the relevant stability parameters were analyzed on at least two experimental (for biological/immunological medicinal products - three series) or industrial series; the applicant has at his disposal satisfactory results of at least a three-month stability study (for biological/immunological medicinal products, six months). Confirmation that studies will be completed and that if the results are not within specification or potentially not within specification at the end of the expiration date, they will be submitted immediately to the competent authority along with a proposed action plan.			
Documentation 1. A change to the relevant section (s) of the dossier, including description, detailed drawing and composition of the container or sealing material, as well as revision of the information on the medicinal product. 2. If applicable, samples of the new container/sealing. 3. Repeated validation studies of sterile products undergoing terminal sterilization have been carried out. Where applicable, the numbers of series used in the validation studies should be given. 4. When changing the free space or the ratio of surface to volume, a declaration that the required stability studies have been started in accordance with the established requirements (indicating numbers of series); and that (if applicable) at the time of implementation of the IA type change notification and the filing of the IB type change notification, the satisfactory results of the stability study are at his disposal; available data do not indicate any problems. Confirmation must also be provided that the studies will be completed and that if the results are not within specification or potentially not within specification at the end of the expiration date, they will be immediately submitted to the competent authority along with a proposed action plan.			
Б.II.д.5 Changing the size of the medicinal product package	Conditions	Required documentation	Type of procedure
а) a change in the number of dosage form units (for			

example, tablets, ampoules, etc.) in the package			
1. The change is within the approved package size range	1, 2	1, 3	IA
2. The change is not within the approved package size range		1, 2, 3	IB
б) change in the size (s) of the package (s)	3	1, 2	IA
в) change in the nominal mass / nominal volume of sterile multi-dose (or single-dose with partial extraction) of parenteral medicinal products and biological / immunological multi-dose parenteral medicinal products			II
г) change in nominal mass/ nominal volume of non-parenteral multi-dose (or single-dose with partial extraction) medicinal products		1, 2, 3	IB
Conditions 1. The new package size must correspond to the dosage regimen and duration of treatment indicated in the general characteristics of the medicinal product. 2. The material of the primary packaging does not change. 3. The remaining forms of release allow to follow the recommendations for dosing and duration of treatment specified in the general characteristics of the medicinal product.			
Documentation 1. A change to the relevant section (s) of the dossier, including revision of information about the medicinal product. 2. Rationale that the new/remaining package sizes correspond to the dosing regimen and duration of treatment indicated in the general characteristics of the medicinal product. 3. Declaration that, if an impact on stability is expected, stability studies will be initiated in accordance with the relevant requirements. Data should be submitted (with a proposed action plan) only if it is not within the specifications.			
Note:	For Б.II.д.5.в) and г) - if the change leads to a change in the “dosage” of the medicinal product, then such a change requires an application for an extension.		
Б.II.д.6 Changing any component of the (primary) packaging that does not directly come into contact with the medicinal product (for example, the color of removable caps, colored code rings on ampoules,	Conditions		Type of procedure

changing the cap that protects the needle (using a different plastic)		Required documentation	
а) a change affecting information about the medicinal product	1	1	IB
б) a change that does not affect information about the medicinal product	1	1	IA
Conditions 1. The change does not affect parts of the packaging material that affect the delivery, use, safety or stability of the medicinal product.			
Documentation 1. A change to the relevant section (s) of the dossier, including revision of information about the medicinal product.			
	Conditions	Required documentation	Type of procedure
а) supplier exclusion	1	1	IA
б) replacement or addition of a supplier	1, 2, 3, 4	1, 2, 3	IB
в) any change in spacer suppliers of metered dose inhaler			II
Conditions 1. There is no exclusion of a packaging component or product. 2. Qualitative and quantitative composition of the packaging/product components and sketch specifications do not change. 3. Specifications and quality control methods are at least equivalent. 4. The sterilization method and its conditions do not change (if applicable).			
Documentation 1. A change to the relevant section (s) of the dossier. 2. Confirmation of the registration of a medical device in the Republic of Kazakhstan in relation to medical devices attached to the medicinal product. 3. Comparison table of current and proposed specifications (if applicable).			
Б.II.д.8 Changing the labeling design of primary and secondary packaging	Conditions	Required documentation	Type of procedure
	1	1,2	IA
Conditions 1. The qualitative and quantitative composition of the packaging / product components and the sketch specifications do not change.			
Documentation 1. A change to the relevant section (s) of the dossier. 2. Packaging layouts in the old design.			

Б.II. e) stability

Б.II.e.1 Changing the shelf life or storage conditions of the medicinal product	Conditions	Required documentation	Type of procedure

а) shortening the shelf life of the medicinal product			
1. Packed in commercial packaging	1	1, 2, 3	IA
2. After the first opening	1	1, 2, 3	IA
3. After dilution or recovery	1	1, 2, 3	IA
б) increase of the shelf life of the medicinal product			
1. Packed in commercial packaging (confirmed by real-time data)		1, 2, 3	IB
2. After the first opening (confirmed by real-time data)		1, 2, 3	IB
3. After dilution or recovery (confirmed by real-time data)		1, 2, 3	IB
4. Increasing the shelf life by extrapolating data on stability that does not correspond to the documents of the Republic of Kazakhstan (*)			II
5. Extending the shelf life of a biological/ immunological medicinal product in accordance with an approved stability study program		1, 2, 3	IB
в) changing the storage conditions of biological / immunological medicinal products, if stability studies were carried out not in accordance with the current approved stability study program			II
г) changing the storage conditions of the medicinal product or the medicinal product after dilution/ recovery		1, 2, 3	IB
д) changing the approved stability protocol	1, 2	1, 4	IB
Conditions 1. The change should not be the result of unforeseen situations that arose during production, or a change in stability. 2. The changes do not lead to an expansion of the acceptance criteria for the test parameters, exclusion of the stability parameter, or a decrease in the frequency of tests.			

Documentation 1. A change to the relevant section (s) of the dossier. It must contain the results of relevant real-time stability studies (covering the declared shelf life), carried out in accordance with the relevant documents of the Republic of Kazakhstan, on three industrial series (1) of the drug packaged using a registered packaging material, and (or) after the first opening or dilution, respectively; where appropriate, microbiological test results should be provided . 2. Revised product information. 3. Copies of approved specifications at the end of the expiration date and, if applicable, specifications after dilution/recovery or after first opening. 4. Rationale of the proposed changes.	
(*) Note:	For a biological/immunological medicinal product, extrapolation is not applicable
(1)	If there is an obligation to check the expiration date on industrial series, experimental series are acceptable.

Б.II. ж) project field and protocol of post-registration changes

Б.II.ж.1 Introduction of a new project field or expansion of the approved project field of the drug (with the exception of biological), affecting:	Conditions	Required documentation	Type of procedure
а) one or more separate operations of the production of the drug, including the corresponding intra - production controls and (or) analytical methods		1, 2, 3	II
б) analytical methods for excipients/intermediate products and (or) drug		1, 2, 3	II
Documentation 1. The results of studies of the development of the drug and the process (including risk assessment and multidimensional studies, respectively), confirming that a holistic mechanistic understanding of the quality indicators of materials and process parameters for the critical parameters of the quality of the drug has been achieved. 2. Description of the project field in a tabular form, including variables (properties of materials and production parameters) and their proposed ranges. 3. The change to the corresponding section (s) of the dossier.			
Б.II.ж.2 Introduction of the post–registration protocol of changes affecting the drug	Conditions	Required documentation	Type of procedure
		1, 2, 3	II
Documentation 1. A detailed description of the proposed change. 2. Protocol of management of changes affecting the drug. 3. The change to the corresponding section (s) of the dossier.			
Б.II.ж. 3 Exclusion of the approved protocol of	Conditions	Required documentation	Type of procedure

management of changes affecting the drug			
	1	1	IA
Conditions 1. The exclusion of the post-registration protocol of management of changes, affecting the drug is not a consequence of unforeseen situations or discrepancy in the specifications during the introduction of the changes described in the protocol and does not affect the approved information included in the dossier.			
Documentation 1. The rationale of the proposed exclusion. 2. The change to the corresponding section (s) of the dossier.			
Б.II.ж.4 Changes in the approved change management protocol	Conditions	Required documentation	Type of procedure
а) significant changes in the change management protocol			II
б) insignificant changes in the change management protocol that do not change the strategy described in the protocol		1	IB
Documentation 1. The declaration that any change should be adjusted to the range of existing approved acceptability criteria. In addition, the declaration that in relation to the biological/immunological drugs an assessment of comparability is not needed.			
Б.II.ж. 5 Implementation of the changes provided for by the approved change management protocol	Conditions	Required documentation	Type of procedure
а) implementation of the change does not require additional auxiliary data	1	1, 2, 4	IA
б) implementation of the change requires additional auxiliary data		1, 2, 3, 4	IB
в) implementation of the change of the biological/ immunological drug		1, 2, 3, 4, 5	IB
Conditions 1. The proposed change was carried out in full compliance with the approved change management protocol requiring immediate notice after its implementation			
Documentation 1. Link to the approved change management protocol. 2. The declaration that the change corresponds to the approved change management protocol and the results of the study satisfy the acceptability criteria agreed in the protocol. In addition, the declaration that in relation to the biological/immunological drugs an assessment of comparability is not needed. 3. The results of studies conducted in accordance with the approved change management protocol. 4. The change to the corresponding section (s) of the dossier. 5. A copy of the approved specifications for the drug.			

Б.II. з Safety in relation to extraneous agents

Б.II.з.1 Update of the Information “Safety assessment related to extraneous agents” (section 3.2.A.2 of the registration dossier)	Conditions	Required documentation	Type of procedure
a) research affecting the production stages, studied for the first time for one or more extraneous agents			II
б) replacing outdated studies affecting production stages and extraneous agents previously included in the dossier			
1. With a change of the risk assessment			II
2. Without a change of the risk assessment		1, 2, 3	IB
Documentation 1. A change to the corresponding section (s) of the dossier, including the introduction of new studies aimed at studying the ability of production stages to inactivate/eliminate extraneous agents. 2. The rationale that studies do not change the assessment of risks. 3. A change to information about the drug (if applicable).			

Б.III Certificate of conformity to European pharmacopoeia (CEP) (if any)/TSE/articles

Б.III.1 Submission of a new or updated certificate of conformity to the European Pharmacopoeia or the exclusion of a certificate of conformity to the European pharmacopoeia	Conditions	Required documentation	Type of procedure
To the pharmaceutical substance, to the source material/reagent/ intermediate product used in the process of production of pharmaceutical substance			
a) a certificate of conformity to the European Pharmacopoeia of the corresponding article of the European Pharmacopoeia			
1. New certificate from a previously approved manufacturer	1, 2, 3, 4, 5, 6, 9	1, 2, 3, 4, 5	IA

2. Updated certificate from a previously approved manufacturer	1, 2, 3, 4, 6	1, 2, 3, 4, 5	IA
3. A new certificate from a new manufacturer (replacement or addition)	1, 2, 3, 4, 5, 6, 9	1, 2, 3, 4, 5	IB
4. Exclusion of certificates (if several certificates were attached to the material)	8	3	IA
5. A new certificate for a non-sterile active pharmaceutical substance to be used in a sterile drug, when using water at the last stage of the synthesis, and the absence of endotoxins in it is not declared in relation to the material		1, 2, 3, 4, 5	IB
б) a certificate of conformity to the European Pharmacopoeia for TSE for an active pharmaceutical substance/source material/ reagent/intermediate product/excipient			
1. A new certificate for an active pharmaceutical substance from a new or previously approved manufacturer	3, 5, 9	1, 2, 3, 4, 5	IB
2. A new certificate for a pharmaceutical substance/ source material/reagent/ intermediate product/ excipient from a new or previously approved manufacturer	3, 6, 7	1, 2, 3, 4, 5	IB
3. Updated certificate from a previously approved manufacturer	7	1, 2, 3, 4, 5	IB
4. Exclusion of certificates (if several certificates were attached to the material)	8	3	IA
5. A new/updated certificate from a previously approved/new manufacturer using materials of human or animal origin, in relation to which an assessment of the			II

risk of potential contamination by foreign agents is needed			
Conditions 1. Specifications for the release and at the end of the expiration date of the drug do not change. 2. Unchanged (excluding tightening) additional (to the State Pharmacopoeia of the Republic of Kazakhstan) specification on impurities (excluding residual solvents, subject to their compliance with the requirements of the Republic of Kazakhstan), product-specific requirements (for example, particle sizes, polymorphic forms), if applicable. 3. The process of production of active pharmaceutical substance, the source material/reagent/intermediate product does not include the use of materials of human or animal origin, for which it is required to analyze viral safety data. 4. Exclusively for active pharmaceutical substance: it will be tested immediately before use if the re-test period is not included in the certificate of conformity to the European Pharmacopoeia or the data substantiating the re-test period is no longer included in the dossier. 5. Active pharmaceutical substance/source material/reagent/intermediate product/excipient are non-sterile. 6. Plant pharmaceutical substances: production method, physical condition, extracting solvent and the coefficient of extraction of the drug do not change. 7. If gelatin made of bones is used in the drug for parenteral administration, its production should be carried out exclusively in accordance with the requirements of the relevant country. 8. At least one manufacturer of this substance remains in the dossier. 9. If the active pharmaceutical substance is non-sterile, but will be used as part of a sterile drug, then, in accordance with CEP, at the last stage of the synthesis, water cannot be used or, if this happens, it is necessary to ensure the absence of bacterial endotoxins in an active pharmaceutical substance.			
Documentation 1. A copy of the existing (updated) certificate of conformity to the European pharmacopoeia. 2. When adding a production site in the form of an application for changes, it is necessary to clearly identify " registered" and "proposed" manufacturers, as indicated in section 2.5 of the application form. 3. The change to the corresponding section (s) of the dossier. 4. If applicable, a document containing information about all materials included in the scope of the article of the State Pharmacopoeia of the Republic of Kazakhstan on minimization of the risk of transmitting agents of spongyform encephalopathy of animals through drugs for medical and veterinary use, including those used in the production of active pharmaceutical substance/excipient. For each such material, it is necessary to present the following information: the name of the manufacturer; the type of animals and fabrics from which the material is obtained; the country of origin of animals and its use. 5. In relation to an active pharmaceutical substance: a declaration of an authorized person of each licensed manufacturer specified in the application using an active pharmaceutical substance as the source material, and the authorized person of each licensed manufacturer specified in the application as a person responsible for the release of the series. In declarations, it is necessary to indicate that the manufacturer (s) of active pharmaceutical substance, specified in the application, carries out their activities in accordance with the Rules of proper production practice of the Republic of Kazakhstan in relation to the source materials. Under certain circumstances , it is allowed to submit one declaration (see note to the change Б.II.б.1). If any updates of certificates for active pharmaceutical substances and intermediate products are affected, an authorized person's declaration is also required from the manufacturers of intermediate products; a declaration of an authorized person is needed only if, in comparison with the previously registered version of the certificate, there is a change in existing ones included in the list of production sites.			
Б.III.2 Changes in order to comply with the State Pharmacopoeia of the Republic of Kazakhstan	Conditions	Required documentation	Type of procedure
a) a change in the specification (s) of the			

earlier non - pharmacopoeial substance in order to comply with the State Pharmacopoeia of the Republic of Kazakhstan			
1. Active pharmaceutical substance	1, 2, 3, 4, 5	1, 2, 3, 4	IB
2. Excipient/source material of active pharmaceutical substance	1, 2, 4	1, 2, 3, 4	IB
б) changes in order to comply with the updated relevant article of the State Pharmacopoeia of the Republic of Kazakhstan	1, 2, 4, 5	1, 2, 3, 4	IB
в) a change in specifications from the State Pharmacopoeia of the Republic of Kazakhstan	1, 4, 5	1, 2, 3, 4	IB
Conditions 1. Change is carried out exclusively for the purpose of complete compliance with pharmacopoeia. All tests in the specification must comply with the pharmacopoeial standard after changing, with the exception of any additional auxiliary tests. 2. Additional specifications for the product-specific properties do not change (for example, particle sizes, polymorphic form or biological methods, units). 3. There are no significant changes in qualitative and quantitative profiles of impurities (with the exception of tightening specifications). 4. An additional primary examination of a new or changed pharmacopoeial methodology is not required. 5. Plant pharmaceutical substances: production method, physical condition, extractant and the extraction coefficient of the drug do not change.			
Documentation 1. The change to the corresponding section (s) of the dossier. 2. Comparative table of current and proposed specifications. 3. The data of the analysis of the series (in the format of the comparative table) of at least two industrial series of the corresponding substance (substance) for all tests of the new specification and additionally, if applicable, the results of the test of comparative dissolution kinetics of at least one experimental series of the drug. In relation to medicinal plant drugs, comparative fragmentation data is sufficient. 4. Data confirming the suitability of an article for the quality control of substance, for example, a comparison of potential impurities with a note of the transparency of the monograph (transparency note of the monograph).			

Б. IV Changing the registration dossier due to other regulatory procedures

Б.V.a.2 The inclusion of a new, updated or corrected master file of the vaccine antigen (hereinafter-MFVA) in the registration dossier of the drug (MFVA procedure of the 2nd stage)	Conditions	Required documentation	Type of procedure
a) the first inclusion of the new MFVA			II

б) inclusion of updated/ corrected MFVA: changes affect the properties of the drug		1, 2, 3, 4	IB
в) inclusion of updated/ corrected MFVA: changes do not affect the properties of the drug		1, 2, 3, 4	IA
Conditions			
Documentation 1. The declaration that the MFVA certificate and the expert report are fully applicable to the registered medicinal drug, the holder of the MFVA presented to the HRC (if HRC and the holder of the MFVA are not the same person) a certificate of the MFVA, an expert report and a dossier for MFVA, the MFVA certificate and the expert report replace the previous documentation for MFVA for this drug. 2. Certificate of MFVA and expert report. 3. An expert declaration characterizing all changes introduced using the certified MFVA and evaluating their potential effect on drugs, including estimates of product-specific risks. 4. In the form of an application for changes, it is necessary to clearly reflect the “current” and “proposed” certificate of MFVA (code number) in the registration dossier. If applied, in the form of an application for changes, all other MFVA that the drug refers to, even if they are not the subject of the application, must be clearly listed.			

B. Changing safety, efficiency and pharmacological supervision

B.I Medical drugs for medical use

B.I.1 Change in the overall characteristics of the drug, labeling of the reproduced/ hybrid/bioanalogical drug after evaluating the same change in the reference drug	Conditions	Required documentation	Type of procedure
а) implementation of the change (s) in respect of which from the holder of the registration certificate it is not required to submit new additional data		1, 2	IB
б) the implementation of the change (s) requiring the presentation by the HRC of additional data substantiating such changes (for example, comparability)			II
Documentation 1. Appendix to the accompanying letter of the application for changes: request of the national authorized body (if applicable). 2. Revised information about the drug (updated brief characteristics of the drug, medical use instructions (leaf-liner).			
B.I.2 Change (s) of the general characteristics of			

the drug, labeling of the drug for medical use, aimed at the implementation of the result of the procedure affecting the PSAR or post-registration study of security	Conditions	Required documentation	Type of procedure
a) the introduction of the wording agreed by the authorized body	1	1	IB
б) making changes requiring the presentation by the HRC of additional data substantiating such changes	2	2, 3, 4	II
Conditions 1. The change implements the wording requested by the authorized body, and does not require the submission of additional information and (or) further examination. 2. The safety of the drug should be preserved and confirmed by clinical studies, clinical security. Confirmations must be provided.			
Documentation 1. Appendix to the accompanying letter of the application for changes: a link to the agreement/assessment of the authorized body. 2. Explanations of the reasons for addition of new warnings of side effects and the statement that the safety of the drug is preserved. 3. Revised information about the drug (updated brief description of the drug, medical use instructions (leaf-liner). 4. A periodically updated security report (PSAR) or post-registration safety study reflecting the changes made.			
B.I.3 Changes, which are a significant change in the general characteristics of the drug due to new quality data, preclinical, clinical data or pharmacological control data	Conditions	Required documentation	Type of procedure
			II
Note:	This change is not applied if new data is submitted in accordance with the change in B.I.13. In such cases, a change in the overall characteristics of the drug, labeling falls under the scope of the application of B.I.13.		
B.I.4 Changing the conditions of the release of the drug	Conditions	Required documentation	Type of procedure
a) reproduced/hybrid/ bioanalogical drugs after changing the conditions of the release of the reference drug	1	1, 2	IB
б) other reasons for changing the conditions of the release	1	2, 3, 4, 5	II

Conditions 1. The safety of the drug should be preserved			
Documentation 1. Confirmation of a change in the conditions of the release of the reference drug, attached to the accompanying letter of the application for changes. 2. Revised information about the drug (updated general characteristics of the drug, medical use instructions (leaf-liner), labeling). 3. Explanation of the reason for changing the conditions of the release and the statement that the safety of the drug is preserved. 4. Data of clinical research, post-registration studies; pharmacological control data. 5. A document confirming a change in the conditions of the release in the country-manufacturer (from the regulatory authority).			
B.I.5 Change (s) of indication (s) for use	Conditions	Required documentation	Type of procedure
a) inclusion of a new indication for the use or change of previously approved	2	1, 2, 3	II
б) exclusion of indications for the use	1	1,2	IB
Conditions 1. The safety of the drug should be preserved and confirmed by retrospective studies, clinical safety and quality. 2. The safety of the drug should be preserved and confirmed by clinical studies, clinical security. Confirmations must be provided.			
Documentation 1. Explanation of the reason for the removal or adding indication and the statement that the safety of the product is preserved. 2. The updated general characteristics of the drug, the instructions for medical use (leaf-liner). 3. Data of clinical research, post-registration studies; pharmacological control data.			
Note	If the addition or change in the indication for use occurs due to the implementation of the conclusion of the expert committee or changes in information about the drug of the reproduced/ hybrid/ bioanalogical drug after examination of the same change in the reference drug, the changes in B.I.1 and B.I.2, are applied, respectively.		
B.I.6 Exclusion:	Conditions	Required documentation	Procedure
a) dosage forms		1, 2	IB
б) dosage		1, 2	IB
Documentation 1. The declaration that the remaining form (s) of the release is sufficient to fulfill the recommendations for dosing and duration of treatment described in the general characteristic of the drug. 2. Revised information about the drug.			
Note	If the dosage form or dosage under consideration were registered in the form of a separate drug, then the exclusion of such a dosage form or dosage will be considered as not making changes, but removal from circulation.		
B.I.7 Introduction or change in the resume of the pharmacological control system of the drug for medical use (*)	Conditions	Required documentation	Type of procedure

a) the introduction of the resume of the pharmacological control system, changes in the qualified person of pharmacological control (including contact information) and (or) a change in the location of the PSMF		1, 2	IB
Documentation 1. The resume of the pharmacological control system or updating of significant elements (respectively): confirmation that the applicant has at his disposal a qualified person responsible for the pharmacological control and approval signed by the applicant that the applicant has the necessary methods for fulfilling tasks and duties in accordance with the established requirements of the current legislation in the field of drug circulation. Contact information of a qualified person of the pharmacological control of the Republic of Kazakhstan, in which a qualified person of pharmacological control is located and performs his tasks Location of the PSMF 2. Number of the PSMF (if any).			
Note:	This change covers the introduction of the PSMF, regardless of the presence in the technical part of the registration dossier of the detailed description of the pharmacological control system. Changes in the contact person for the pharmacological control, including contact information (phone numbers and faxes, mailing address and email address) and changes in the location of the PSMF (street, city, index, country) are allowed to be updated exclusively through the register of the Republic of Kazakhstan (hereinafter - the Register of the Republic of Kazakhstan) (without the need to make changes). If the holder of the registration certificate resorts to the possibility of updating the above information using the Register of the Republic of Kazakhstan, he must indicate in the registration dossier that the updated information of these data is included in the Register of the Republic of Kazakhstan.		
B.I.8 Change in the existing system of pharmacological control according to a detailed description of the pharmacological control system (hereinafter - the DDPCS)	Conditions	Required documentation	Type of procedure
a) a change in a qualified person for pharmacological control and (or) contact information, and (or) reservation procedures	1	1	IB
б) a change in the security database and (or) basic contract agreements in order to fulfill pharmacological control obligations and (or) a change in the venue	1, 2, 3	1	IB

в) other changes in the DDPCS that do not affect the functioning of the pharmacological control system (for example, a change in the location of the main storage/archive, administrative changes)	1	1	IB
г) making changes to the DDPCS based on the results of the DDPCS examination of another drug of the same HRC	4	1, 2	IB
Conditions 1. The pharmacological control system itself does not change. 2. The database system was validated (if applicable). 3. The transfer of data from other database systems is valid (if applicable). 4. The same changes in the DDPCS are introduced for all drugs of the same HRC (the same final version of the DDPCS).			
Documentation 1. The latest version of the DDPCS and, if applicable, the latest version of the drug-specific addition. They should, regarding a change in a qualified person for pharmacological control, include: a) a brief biography of a new qualified person for the pharmacological control, b) a new position of the holder and a qualified person for the pharmacological control about their ability and notification of unwanted reactions, signed by a new qualified person for the pharmacological control and the holder, and reflecting the remaining arising changes, for example, in the organizational scheme. If a qualified person for the pharmacological control and (or) contact information of a qualified person for pharmacological control was not originally included in the DDPCS or there is no the DDPCS, the submission of the revised DDPCS is not required, it is necessary to submit only the application form. 2. The link to the application/procedure and the drug in respect of which the changes were approved.			
B.I. 9 Changing the frequency and (or) date of submitting a periodic security report (DDPCS) of drugs for medical use	Conditions	Required documentation	Type of procedure
	1	1, 2	IB
Conditions 1. Changing the frequency and (or) the date of submission of the DDPCS is agreed by the national authorized body.			
Documentation 1. Appendix to the accompanying letter of the application for changes: a link to the agreement of the authorized body. 2. Reviewed frequency and (or) the date of filing of the DDPCS.			
Note	This change is applied only if the cycle of the DDPCS is indicated in the registration dossier in ways, different from indicating the link to the list of reporting dates, and if necessary, the submission of the DDPCS.		
B.I.10 Introduction or changes in obligations and	Conditions		Type of procedure

registration conditions, including the risk management plan		Required documentation	
a) the implementation of the wording agreed with the authorized body	1	1, 2	IB
б) the implementation of changes requiring the submission by the HRC of additional data that needs an examination by an authorized body (*)			II
Conditions 1. The change implements the action requested by the authorized body, and does not require the submission of additional information and (or) further examination			
Documentation 1. Appendix to the accompanying letter of the application for changes: a link to the corresponding decision of the authorized body. 2. Revised information about the drug.			
Note	This change covers only the situation in which the introduced change affects the conditions and (or) registration obligations exclusively, including the risk management plan and (or) conditions and (or) registration obligations under exceptional circumstances and conditional registration		
(*)	the introduction of a risk management plan, requested by the authorized body, always requires a significant examination		
B.I. 11 The inclusion or exclusion of a black symbol or explanatory instructions regarding drugs included in the list of drugs subject to additional monitoring	Conditions	Required documentation	Type of procedure
	1	1, 2	IB
Conditions 1. The drug is included or excluded from the list of drugs subject to additional monitoring (respectively).			
Documentation 1. Appendix to the accompanying letter of the application for changes: a link to the list of drugs subject to additional monitoring. 2. Revised information about the drug (updated general characteristics of the drug, medical use instructions (leaf-liner).			
Note	This change covers a situation in which the inclusion or exclusion of a black symbol or explanatory instructions is not carried out within the framework of another regulatory procedure (for example, extension or change procedures that affect information about the drug)		
B.I.12 Other changes not described in other sections of this Addition, including the submission of studies to the authorized body (*)	Conditions	Required documentation	Type of procedure
			II

Note	If the examination by the authorized body of the data presented leads to a change in the general characteristics of the drug, labeling, this change covers the corresponding changes to the general characteristic of the drug, and labeling.
(*)	This change is not applied to changes that are adopted as changes of the IB type by default in accordance with any other section of this Addition.

Note:

When making changes to the registration dossier of type II:

- by paragraphs Б.I, a list of documents of sections I, II of the list (updated sections I A7 - a document confirming the quality of the active substance (certificate of analysis of 3 series of active pharmaceutical substance from the manufacturer, certificate of analysis of the substance from the manufacturer, certificate of compliance with the monograph of European pharmacopeia, protocol of analysis, analytical passport, data on the study of the stability of the finished product under long-term and accelerated conditions for the study of stability using the declared substance for at least 6 months) and II C 1 - active substance in accordance with the changes made) is provided.

- by paragraphs Б.II, a list of documents of sections I (updated section I A8 - a document confirming the quality of the finished product of 3 industrial series (analysis certificate, protocol of analysis), one series of which coincides with the series of the sample of the drug submitted for registration in accordance with the changes made) and II list are provided.

Appendix 7
to the Rules of temporary
state registration of
vaccines against
COVID-19
Form

Footnote. The rules are supplemented by Appendix 7 in accordance with the resolution of the Government of the Republic of Kazakhstan dated 15.04.2021 No. 244.

Conclusion on changes to the registration dossier of the vaccine

1. The expert commission reports the results of the examination for safety, quality and effectiveness of the vaccine for the purposes of temporary state registration in the Republic of Kazakhstan:

Number and date of application	
The trade name of the vaccine (indicating the dosage form, dosage, concentration and volume of filling, the number of doses in the package - for the drug)	
Organization-manufacturer, country-manufacturer, holder of a temporary registration certificate	
Type of changes made	
The conclusion of the expert commission (positive or negative)	

2. Conclusion (positive): materials and documents of the registration dossier to the vaccine presented to make changes to the registration dossier meet the requirements of the Rules of temporary state registration of vaccines against Covid-19, (hereinafter-the Rules).

The changes made can be registered.

Conclusion (negative): materials and documents of the registration dossier to the vaccine, presented to make changes to the registration dossier, do not meet the established requirements of the Rules.

The changes made cannot be registered.

Head of the expert commission

_____ _____

signature name, surname, patronymic (if any)

Members of the expert commission

_____ _____

signature name, surname, patronymic (if any)

_____ _____

signature name, surname, patronymic (if any)

_____ _____

signature name, surname, patronymic (if any)