THE EURASIAN ECONOMIC COMMISSION
BOARD

R E C O M M E N D A T I O N

September 26, 2017 **No 19** Moscow

On Guideline on Validation of the Production Process of Medicinal Products for Medical Use

The Board of the Eurasian Economic Commission, in accordance with Article 30 of the Treaty on the Eurasian Economic Union dated May 29, 2014, paragraph 3 of Article 3 of the Agreement on Common Principles and Rules of Circulation of Medicinal Products within the Eurasian Economic Union dated December 23, 2014,

in order to harmonize the requirements to validation of pharmaceutical production processes established by the legislation of the Member States of the Eurasian Economic Union,

r e c o m m e n d s that the Member States of the Eurasian Economic Union, upon expiration of 6 months from the date of publication of this recommendation on the official website of the Eurasian Economic Union, apply the Guideline on validation of the production process of medicinal products for medical use, according to the Annex hereto, when manufacturing medicinal products for medical use, preparing registration dossiers for registration of medicinal products in accordance with the Rules of registration and examination of medicinal products for medical use, approved by the Decision of the Council of the Eurasian Economic Commission No. 78 dated November 3, 2016, bringing the registration dossiers of medicinal products in accordance with the said Rules and inspecting production sites for compliance

with the Rules of good manufacturing practices of the Eurasian Economic Union, approved by the Decision of the Council of the Eurasian Economic Commission No. 77 dated November 3, 2016.

Chairman of the Eurasian Economic
Commission Board T. Sargsyan

ANNEX
to the Recommendation of the
Board of the Eurasian Economic
Commission No. 19
dated September 26, 2017

GUIDELINE
on Validation of the Production Process of Medicinal Products for Medical Use

I. Introduction

1. This Guideline constitutes rules for documenting the results of confirming that the production process executed within the prescribed parameters effectively and reproducibly ensures obtaining the medicinal product corresponding to the established specifications and quality attributes, to represent them in the registration dossiers of the medicinal product.

2. By introducing continuous process verification, an alternative approach to process validation is determined on the basis of continuous monitoring of the production process. This approach is based on the knowledge of the product and process, obtained during their development and/or through the experience of previous production. Continuous process verification can be applied to both traditional and advanced approaches to pharmaceutical development. To evaluate a process, methods of continuous monitoring and/or control can be used. It is believed that the totality of the provisions contained in the guidelines on pharmaceutical development adopted by the Eurasian Economic Commission, and this Guideline, covers all critical stages of the technological process that should be included in the registration dossier of a medicinal product for medical use, according to Annex No. 1 to the Rules of registration and examination of medicinal products for medical use approved by the Decision of the Board of the

Eurasian Economic Commission No. 78 dated November 3, 2016 (hereinafter – registration dossier, Rules for registration and examination, respectively).

3. Process validation should not be regarded as a one-time event. The approach to validation based on the process life cycle includes development of the product and the process, validation of the industrial scale manufacturing process and maintenance of the process in a controlled condition during routine industrial production.

II. Scope of application

4. This Guideline defines the composition of information on process validation which must be submitted when registering a medicinal product of chemical nature for medical use. General principles related to validation are also applicable to active pharmaceutical substances. It is generally not required to provide information on validation of the production process of non-sterile pharmaceutical substances in the registration dossier. The requirements to validation of production of active pharmaceutical substances are set out in greater detail in the Guideline «Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)» of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICHQ11).

The principles contained in this Guideline apply to biological medicinal products. Due to the complexity and variability inherent to biological substances, production process validation of such medicinal products must be considered individually.

5. The information required in accordance with this Guideline is presented in the registration dossier at the time of filing the application for the registration of the medicinal product to the authorized body of the Member

State of the Eurasian Economic Union in the sphere of circulation of medicines (hereinafter, respectively, the authorized body, the Member State).

6. Validation of the production process in accordance with this Guideline is regarded as the second stage of the process life cycle. The first stage (process development) is dealt with in pharmaceutical formulation guidelines, the third phase (current process verification) is dealt with in Annex No. 15 to the Rules of good manufacturing practices of the Eurasian Economic Union, approved by the Decision of the Council of the Eurasian Economic Commission No. 77 dated November 3, 2016 (hereinafter - the Rules of good manufacturing practices).

III. Definitions

7. For the purposes of this Guideline, the following terms shall be used, their meanings set forth in the respective definitions below:

«process validation» is a documented confirmation that the production process executed within the prescribed parameters effectively and reproducibly ensures obtaining the medicinal product corresponding to the earlier established specifications and quality attributes;

«product lifecycle» means all stages of the product life from initial development, circulation, and until the product ceases to exist;

«bracketing» is a scientific approach based on risk assessment and set out in the process validation plan, justifying the possibility to only test batches with extreme values of some factors in process validation, for example, with a certain dosage, batch size and/or packaging capacity. This approach assumes that validation of any intermediate values of factors is presented as validation of extreme values. Bracketing can be applied for a range of dosages subject to validation, if such dosages are identical or very similar in formulation, e.g., for

tablets obtained with different pressing efforts from a similar granulate or to a number of capsules with different capacity filled with identical amount of content. Bracketing can be applied to containers with varying capacity or varying filling volume of the same container closure system;

«critical process parameter, CPP» is a process parameter, the variability of which affects critical quality attributes and which, therefore, is subject to monitoring or control to ensure the required quality as the result of process implementation;

«critical quality attribute; CQA» is a physical, chemical, biological or microbiological property or characteristic, that must remain within the corresponding limits and range or have proper distribution in order to ensure the required quality of the product;

«in-line method» is a measurement method in which a sample is analyzed directly in the process flow and is not removed from it;

«on-line method» is a measurement method in which a sample is removed from the process flow with a chance to be returned into the process flow;

«at-line method» is a measurement method in which a sample is removed from the process flow, isolated from it and analyzed in a close proximity to the flow;

«continuous process verification» is an alternative approach to process validation in which the production process is constantly monitored and evaluated;

«design space» is a polydimensional combination and interaction of input variables (e.g., material quality attributes) and process parameters which confirmed the ability to ensure the quality of the product. Operation within the design space is not considered a change. Going beyond the design space is

considered a change and usually requires approval of the changes after their coordination with the authorized body. Design space is proposed by the person who submits an application for the registration of the medicinal product, and is subject to evaluation and approval by the authorized body;

«enhanced approach» is an approach to process development based on the use of scientific knowledge, study results and risk assessment to identify and understand the characteristics of materials and process parameters affecting the critical quality attributes of the product;

«control strategy» is a planned complex of control elements, developed based on the current understanding of the product and process, that ensures suitability of the process and product quality. Control elements can include parameters and characteristics associated with active pharmaceutical substances and medicinal products, materials and components, operating conditions of premises and equipment, in-process control, finished product specifications, techniques and periodicity of monitoring and control;

«traditional approach» is an approach to product development, which establishes specific values and operational ranges of process parameters to ensure reproducibility;

«pharmaceutical quality system; PQS» is a control system to direct and control a pharmaceutical company with regard to quality.

IV. General provisions

8. Regardless of the approach used during the development of the medicinal product, traditional or enhanced, prior to the release of the medicinal product on the market its production process must be validated. On extraordinary occasions (in case of a «benefit-risk» ratio particularly favorable for the patient) it is allowed to conduct a relevant validation.

9. Process validation must confirm that the process within the developed control strategy is able to ensure the quality of the product. Validation must cover all dosage intended for release and all production sites used for the production of the market product. For different dosages, batch sizes and packaging capacities, bracketing can be acceptable, however, validation must be performed on all of the proposed production sites. Data on process validation must confirm the suitability of the process for all products and at each production site. Validation must be conducted in accordance with the requirements of the Rules of good manufacturing practices, the data obtained must be kept at the place of production and be available for inspection, if their representation in the registration dossier is not required (pursuant to Section VIII of this Guideline).

10. Regardless of the approach used in developing the process, its validation can be performed using the traditional method. Continuous process verification may be used if the process was developed using the enhanced approach, or a considerable amount of knowledge about product and process was obtained on the basis of historical data and production experience. A combination of traditional validation and continuous process verification may be used. When monitoring incorporates «in-line», «on-line», «at-line» methods frequently used in continuous process verification (in accordance with subsection 2 of Section V of this Guideline), it provides much more information and knowledge of the process and can improve the process.

V. Process validation

1. Traditional process validation

11. Traditional process validation is usually conducted upon completion of pharmaceutical development and/or process development after scaling the production process and prior to the release of the finished product. Within the life cycle of the product, some studies on production process validation can be performed on pilot batches before scaling the process. It should be noted that the size of the pilot batch must correspond to at least 10% of the size of an industrial scale batch (i.e. the scaling factor must not exceed 10). For solid oral dosage forms the size of the pilot batch, as a rule, should amount to at least 10% of the maximum amount of an industrial scale batch or 100,000 units, whichever number is greater.

If the estimated size of the production batch is less than 100,000 units, the predictive value of validation results obtained on pilot batches can be limited, and the use of this approach must be justified. For other dosage forms, the size of the pilot batch must be justified taking into account the risk for the patient resulting from the inconsistency of quality for this dosage form.

12. Conducting full validation studies on pilot batches is generally considered unfeasible, therefore, for each medicinal product a process validation plan should be developed (in accordance with the requirements according to Annex No. 1), with subsequent validation on industrial-scale batches, and also bracketing can be applied. Process validation plan should be included in the registration dossier. Process validation plan must include a description of the production process, the list of tests performed and the acceptance criteria, a description of additional controls in the process, as well as the data that must be obtained. Justification of the process validation plan

must be presented in Section 2.3 («Overall quality summary») of Module 2 of the registration dossier. Information on process validation at the moment of applying for the registration of the medicinal product shall be submitted for the production process on an industrial scale for non-standard products (for example, biological (biotechnological) products), or in case a non-standard production method is proposed (in accordance with Section VIII of this Guidance and in accordance with Annex No. 2).

In such cases, the data on the series of successive industrial scale batches must be submitted to the authorized body (expert organization) of the reference state, determined in accordance with the Rules of registration and examination, within 14 working days after receiving the opinion on Module 3 of the registration dossier. The number of batches must be justified on the basis of process variability, complexity of the process (product), knowledge about the process, obtained during the development, supporting data obtained on an industrial scale during technology transfer and general experience of the manufacturer. Validation data must be submitted for at least 3 industrial scale batches, unless a different number of batches is justified. Data for one or two industrial scale batches may be sufficient subject to available data on pilot batches and appropriate justification (as described above).

13. Validation studies should include the critical stages of the process, as well as additional tests (if necessary).

2. Continuous process verification

14. As an alternative to the traditional process validation, continuous process verification can be used, in which the process is continuously monitored and evaluated. Continuous process verification can be used in addition to the traditional process validation or replace it.

Continuous process verification is a scientific approach based on risk assessment, used to verify and validate in real time that the process performed within the established parameters according to the approved documentation constantly ensures obtaining the product complying with all critical quality attributes and requirements of the control strategy.

15. For the manufacturer (applicant), using continuous process verification means conducting an extensive process monitoring using "in-line», «on-line», «at-line» methods, controlling product quality and suitability of the process for each batch. You must get the corresponding data on quality attributes for the source materials or components, intermediate products and the finished product. Data should also include verification and assessment of critical quality attributes (CQAs) and critical process parameters (CPPs), including the assessment of trends. As tools for practical implementation of continuous process verification, it is possible to use such process analytical technologies (PAT) as spectroscopy in the near infrared spectrum (for example, to determine the homogeneity when mixing, surface area of the granules, the homogeneity of content for large size samples) and multivariate statistical process control (SPC).

16. The scale and degree of application of continuous process verification depends on several factors, including the following:

a) the availability of prior knowledge of development and production of similar products and/or processes;

b) the degree of understanding the process (detailing and extensive documentary description), obtained during studies in its development and as a result of the experience of production on industrial scale;

c) the complexity of the product and/or production process;

d) the level of process automation and the process analytical technologies (PAT) used;

e) information based on the product life cycle, sustainability of the process and experience of production on an industrial scale for the existing products (if necessary).

17. The justification of suitability and feasibility of continuous process verification must be included in subsection 3.2.P.2. («Pharmaceutical development») of Module 3 of the registration dossier and confirmed by the data from laboratory or pilot batches. The description of the continuous process verification system, including controlled process parameters and attributes of materials, the monitoring analytical techniques used, must be included in the registration dossier with a cross-reference to the «Validation» Section (in accordance with Annex No. 1 to this Guideline). The actual data obtained in the course of continuous process verification of industrial scale production must be available when conducting an inspection of the production site. The applicant must determine and justify the selection of the critical stages of the process and complete validation studies prior to the release of the product. It is necessary to provide a justification of the number of batches of the product which will be used for the process validation depending on the complexity and the expected variability of the process and the available production experience. Continuous process verification is considered to be the most appropriate method to validate continuous processes.

18. Continuous process verification may be introduced at any stage of the product life cycle. This approach can be used in the following cases: during the initial production on industrial scale, to verify validated processes as part of the change control procedure and to support the process of continuous improvement.

19. Continuous process verification is carried out in accordance with the principles and requirements of the Rules of good manufacturing practices. Pharmaceutical quality systems (PQS) may complement the requirements of the Rules of good manufacturing practices. However, the issues related to the procedure of complying with the Rules of good manufacturing practices and pharmaceutical quality systems should not be included in the registration dossier, because assessment of these issues is performed when inspecting production of medicinal products for compliance with the requirements of the Rules of good manufacturing practices.

3. Combined approach

20. It is allowed to use a combined approach which consists in applying the traditional approach to validation and continuous process verification for various stages of production. The registration dossier must clearly specify which validation approach was used at various stages of the production process. The number of batches and batch size required for validation will depend on the degree of using the continuous process verification. If continuous verification process is not used for the critical operations of non-standard processes (as specified in Section VIII of this Guideline), the requirements to process validation shall apply in accordance with subsection 1 of Section V of this Guidance in the absence of other justification.

4. Design space verification

21. Design space is usually developed on the basis of laboratory or pilot batches. When scaling, an industrial process is usually carried out and validated in the corresponding design space, which is defined as the target interval or normal operating range. During the product life cycle, changing

parameters and characteristics of the process within the design space (i.e. within the operating ranges of the process and quality attributes of materials) can lead to higher risks or risks not identified during the development. For this reason, and also depending on how the design space was initially defined and the process validated, it may be necessary to confirm the suitability of the new area in the design space (by providing evidence that all quality attributes of the product meet the criteria), i.e. to verify the design space.

22. If it has not been shown that the parameters examined when developing the design space can be scaled regardless of the production scale, and the process was validated using the traditional approach, it will be necessary to verify the design space and to include a protocol of such verification in the registration dossier. Using continuous process verification can contribute to confirmation of the suitability of the design space within the product life cycle. In this case, verification of the design space should be considered as part of the continuous process verification system.

23. Depending on the variability of parameters and characteristics of the process and their movement within the design space (i.e. oscillations within the optimal operating parameters (validated ranges) or in a new area of the design space with a higher or unknown risk emerging), verification plan may include quality attributes (QAs), and process parameters (PPs), not included in the routine process monitoring system (for example, monitoring or testing QAs and PPs, which may depend on the scale of production and (if applicable) on the equipment). There is no need to verify all areas of the design space or permissible ranges of the design space.

24. More than one area of the design space must be verified, but a step-by-step approach to adjust the approved design space during the product's life cycle is also acceptable.

VI. Scaling

25. To avoid lengthy and expensive testing, collection of information and data on the progress of studies in developing, optimizing and scaling the process must be properly organized. This information is provided to justify that process scaling can be achieved without loss of quality when carrying out an industrial production process. Subsection 3.2.P.2 («Pharmaceutical development») of Module 3 of the registration dossier must specify the elements of the process that will prove critical when scaling, subsection 3.2.P.3 («Production process of the medicinal product») of Module 3 of the registration dossier must contain their description.

26. If batch sizes are proposed in certain ranges, a justification must be provided that resizing a batch will not have a negative impact on critical quality attributes (CQA) of the finished product. The parameters set out in the process validation plan (in accordance with Annex No. 1 to this Guideline), must be checked again when resizing the batch, if no evidence is provided that the process is independent of the scale, or if continuous process verification is not used.

VII. Post-registration change control

27. It is necessary to establish clear procedures to manage changes proposed for the production process. Such procedures are part of the requirements of the Rules of good manufacturing practices and are usually not specified in the registration dossier. Change control procedures must ensure that sufficient data is collected using an approved control strategy, to confirm that the modified process allows for obtaining the product of the desired quality and ensuring complete and detailed documentation and approval of all

elements associated with the change, including the assessment of the need to introduce changes in the registration dossier.

Detailed information on the changes that must be introduced in the registration dossier is given in Annexes No. 19 and 20 to the Rules of registration and examination.

VIII. Standard and non-standard production processes

28. The provisions of this Section only apply to processes which have been validated using the traditional approach, and not to processes that use continuous process verification (in accordance with subsections 1 and 2 of Section V of this Guideline). In accordance with subsection 1 of Section V of this Guideline, when scaling production, data must be submitted in the registration dossier for non-standard products or non-standard processes validated using the traditional approach. The applicant may give a justification that the product manufacturing process is standard for a specific production (production site), taking into account the risk for the patient caused by inconsistency in the quality of the medicinal product or process. Such justifications are assessed in each case, but the information provided by the applicant (for each production site) should include:

a) experience with the same or similar product or process (list of products registered (sold) on the territories of the Member States, and the number of batches produced (including their size));

b) product name (number of registration certificates) in the Member State concerned;

c) the amount of knowledge stored during product development (the number and size of the batches produced at each production site);

d) historical data on compliance with the requirements of the production sites with the Rules of good manufacturing practices for this type of process.

29. When applying for registration, the applicant must indicate the category of the production process (standard or custom) in Section 3.2.P.3.5 ("Validation of the production process and/or its evaluation") of Module 3 of the registration dossier, and justify why this category was selected.

Additional information on products (processes), regarded as non-standard, is given in Annex No. 2 to this Guideline.

ANNEX No. 1
to the Guideline on Validation of
the Production Process of
Medicinal Products for Medical
Use

REQUIREMENTS
to the process validation plan

I. Traditional process validation

1. If traditional process validation is intended in accordance with subsection 1 of Section V of the Guideline on validation of the production process of medicinal products for medical use (hereinafter referred to as the Guideline) under the conditions of insufficient data obtained from industrial scale batches, the applicant submits a process validation plan to the authorized body of the Member State of the Eurasian Economic Union in the sphere of circulation of medicinal products (hereinafter referred to as the authorized body). It specifies the amount and order of implementation of validation studies, which will be conducted on industrial scale batches (the number of batches for validation will depend on the variability of the process, complexity of the process and product, as well as on the experience of the manufacturer, but usually it is at least 3 consecutive batches). Information on these studies should be available to the authorized bodies for post-registration inspection.

Process validation plan is included in the registration dossier provided for in Annex No. 1 to the Rules of registration and examination of medicinal products for medical use, approved by the Decision of the Council of the Eurasian Economic Commission No.78 dated November 3, 2016 г., and contains, among other things:

a) a brief description of the process with indication of critical stages of production or critical process parameters subject to monitoring while conducting validation;

b) specification on the release of the finished product (references to the corresponding Section of the registration dossier);

c) detailed information about analytical techniques (references to the relevant techniques specified in the registration dossier);

d) information about in-process control and the acceptability criteria;

e) information on the proposed additional tests (with the acceptability criteria and validation of analytical techniques (where appropriate));

f) sampling plan (indicating the time, place and method of sampling);

g) methods of accounting and evaluating the results;

h) the proposed schedule for conducting studies.

2. The results of the validation performed must be documented, signed by a duly authorized person and be available for inspection.

3. The report on the validation performed must contain the following information:

a) test results of product batches;

b) product analysis certificates;

c) product batches production protocols;

d) information about unexpected results received, deviations or changes introduced (with justifications);

e) conclusions.

4. When receiving significant deviations from the results expected, the applicant shall immediately notify the authorized bodies indicating the corrective actions. All the proposed changes in the production process must get approval through introducing changes in the registration dossier.

II. Continuous process verification

5. When continuous process verification is intended (in accordance with subsection 2 of Section V of the Guideline), the applicant submits a continuous process verification plan, which includes a description of the monitoring of industrial batches. The information submitted must be available to the authorized bodies for post-registration inspection.

6. The continuous process verification plan is included in the registration dossier and (where necessary) contains the following information:

a) a detailed description of the use of monitoring to control process parameters by an «in-line» («on-line», «at-line») method (including monitoring frequency, number and size of the samples checked);

b) information about analytical techniques (references to the relevant techniques specified in the registration dossier);

c) acceptance criteria;

d) information, including, where appropriate, justification of the ability of continuous verification to maintain control of reproducibility of the process during production of the product on an industrial scale, as well as information about statistical data processing methods applied;

e) justification of how monitoring will contribute to the verification of the design space (when developing the design space).

ANNEX No. 4
to the Guideline on Validation of
the Production Process of
Medicinal Products for Medical
Use

INSTRUCTIONS
for determining standard and non-standard processes

I. General provisions

1. Processes are qualified as standard or non-standard on the basis of the assessment of the nature of the pharmaceutical substance, nature of the finished product, the production process and the experience of the manufacturer.

All biological products are regarded as non-standard.

2. Products or processes that may be considered as non-standard, and for which validation data of industrial scale batches are given in the registration dossier (in the absence of other justification), include:

a) production of specialized dosage forms;

b) inclusion of some new technologies in the normal process;

c) specialized processes using new technologies or complex processes that require special care;

d) non-standard methods of sterilization.

3. Technological operations during the production process of medicinal products that had not previously been used within the framework of the Eurasian Economic Union, generally regarded as non-standard.

II. Specialized dosage forms

4. The types of products that are regarded as specialized, include:

a) medicinal products for dosed introduction into the lungs (for example, aerosol dosing inhalers and dry powder inhalers);

b) sterile suspensions, emulsions or other dispersed sterile fluids;

c) medicinal products with modified release;

d) single-dose medicinal products with a low content of the active substance (< 2% of the ingredients);

e) other specialized dosage forms (i.e., parenteral depots based on biodegradable polymers, liposomes, micelles, nanoparticles).

III. Routine pharmaceutical processes, incorporating new technologies

5. Properly designed and approved routine pharmaceutical processes can, for example, include the pelletization stage using wet granulation. However, introduction of a new technological operation into the normal process (for example, a new drying technology), not normally used in the pharmaceutical industry, may lead to the need for comprehensive validation based on the data obtained during the development of the process and product.

IV. Specialized or complex processes

6.Specialized or complex processes include:

a) processes including such critical stages as lyophilization, microencapsulation;

b) processes in which the physical and chemical properties of the active pharmaceutical substance or key excipient (e.g. lubricants, agents for coating) can lead to difficulties when processing or scaling production, or any problems related to maintaining stability when carrying out a process on an industrial scale;

c) aseptic processes.

V. Non-standard methods of sterilization

7.Non-standard methods of sterilization include:

a) final moist heat sterilization using non-pharmacopoeial sterilization modes;

b) final sterilization by ionizing radiation with the absorbed dose less than 25 kGy.