ANNEX

to Decision No.
of the Eurasian Economic Commission's Council
dated 20

AMENDMENTS
to the Rules of Good Manufacturing Practice of the Eurasian Economic Union

1. The following sentence shall be added to indent 3, Subsection 1.2, Part II of the above-mentioned Rules: "Section 17 contains recommendations for parties who (in addition to other pharmaceutical activities) perform distribution or storage of active pharmaceutical ingredients or intermediate products. These Rules are supplemented with recommendations regarding the principles of good distribution practice for active pharmaceutical ingredients utilized in drug products for human use".

2. The term "design space" in Section 5, Chapter 3, Part III of the above-mentioned Rules shall be described as follows: *design space* means a multi-dimensional combination of input variables (e. g., characteristics of materials and manufacturing process parameters ensuring quality). The manufacturing process within the design space cannot be considered as a change. Going beyond the design space is considered as a change and usually requires the initiation of the process of regulatory post-registration changes. The design parameter space is proposed by the applicant and is subject to regulatory assessment and approval;".

3. Annex No. 15 to the above-mentioned Rules shall be set out as follows:

"Annex No. 15

to the Rules of Good Manufacturing Practice of the Eurasian Economic Union

REQUIREMENTS
for qualification and validation

Principle

1. This Annex describes the principles of qualification and validation applicable to premises, equipment, utilities and processes used in production of pharmaceuticals, and may be partially used as additional guidelines for active pharmaceutical ingredients without introducing additional requirements to those set out in Part II of the Rules of Good Manufacturing Practice of the Eurasian Economic Union approved by Decision No. 77 of the Eurasian Economic Commission's Council dated November 3, 2016 (hereinafter referred to as the Rules). According to the Rules, the manufacturer shall control all critical aspects of its specific activities by means of qualification and validation of equipment and manufacturing processes throughout the product lifecycle and manufacturing period. Any prearranged changes in premises, equipment, utilities and manufacturing processes that may affect the product quality shall be properly documented. Their impact on the corresponding validation status or control strategy shall be assessed. The computer systems used in the manufacturing of finished products shall also be validated according to the requirements specified in

Annex No. 11 to the Rules. The relevant concepts and recommendations presented in Chapter II and Chapter III, Part III of the Rules shall also be taken into account.

General information

2. The quality risk management approach shall be used throughout the product lifecycle. As part of the quality risk management system, the decisions on limits and scope of validation and qualification shall be based on justified and properly documented assessment of the risks related to premises, equipment, utilities and manufacturing processes. Retrospective validation is no longer considered an acceptable approach. The data supporting qualification and (or) validation studies, which were obtained from sources outside of the manufacturer's own validation program, may be used provided that this approach has been justified and that there is adequate assurance that controls have been in place throughout the process of acquisition of such data.

1. Organization and planning of qualification and validation

3. All qualification and validation procedures shall be planned while taking into account the lifecycle of premises, equipment, utilities, manufacturing processes and products.

4. Qualification and validation shall be performed by properly trained staff following the approved procedures.

5. The reporting line of the staff responsible for qualification and validation shall correspond to the order established in the pharmaceutical quality system. The qualification and validation functions are not necessary to be performed solely by quality assurance and quality control services.

However, appropriate control shall be ensured by quality assurance and quality control services during the entire validation cycle.

6. The key components of the company's qualification and validation program shall be clearly defined and properly documented in the validation master plan (VMP) or an equal document.

7. The validation master plan (VMP) or an equal document shall define the qualification and validation system or contain references at least to the following information:

а) qualification and validation policy;

б) organizational structure including the roles and responsibilities for qualification and validation processes;

в) a brief overview of the company's premises, systems, equipment and processes, as well as the current qualification and validation status;

г) management (control) of changes and management of deviations during the qualification and validation process;

д) guidelines on the development of acceptance criteria;

е) references to the existing documents;

g. qualification and validation strategy including re-qualification, where applicable.

8. In case of large and complex projects, planning becomes of special importance; there may be a need to develop a number of individual validation master plans.

9. The quality risk management approach shall be used for qualification and validation.

10. Taking into account the experience and information obtained during the process design and pharmaceutical product manufacturing, there may be a need for re-assessment of quality risks. The use of quality risk

assessment for qualification and validation services shall be properly documented.

11. An acceptable control of qualification and validation shall be implemented to ensure the integrity of all implemented data.

2. Documentation

12. The rules of proper documenting are required to maintain the corresponding knowledge management process throughout the product's lifecycle.

13. All documents created during qualification and validation shall be agreed and approved by relevant staff members as specified by the pharmaceutical quality system.

14. The relation between the documents in complex validation processes shall be clearly defined.

15. The validation protocols under development shall define critical systems, indicators and parameters, as well as the corresponding acceptance criteria.

16. Qualification documents may be joined together where applicable (e. g., for installation qualification (IQ) and operation qualification (OQ)).

17. If validation protocols and other documentation are delivered by a third party providing validation services, the relevant manufacturing facility staff shall check the suitability of the validation protocols and their compliance with internal procedures of the pharmaceutical manufacturer prior to the approval of the validation protocols. Prior to their use, the validation protocols from validation service providers may be supplemented with documentation and test protocols.

18. Any major changes in the approved validation protocol during its execution (e. g., acceptance criteria, functioning parameters, etc.) shall be documented as deviations with the corresponding scientific rationale.

19. The results that fail to comply with the established acceptance criteria shall be recorded as deviations and completely investigated according to the internal procedure. Any possible consequences for validation shall be reflected in the validation report.

20. The validation report and conclusions shall be recorded, and the obtained results shall be compared with the acceptance criteria. Any subsequent changes in the acceptance criteria shall be provided with a scientific rationale, and final recommendations shall be developed following the results of validation.

21. A formal transfer to the subsequent qualification and validation stage shall be confirmed by the relevant responsible staff members (either at the validation report approval stage or in the form of a separate umbrella document). A nominal approval of the transfer to the next stage is possible in case of partial consideration of specific acceptance criteria or deviations, if they are properly assessed and documented as having no major impact on the subsequent procedures.

3. Qualification stages for equipment, premises, utilities and other systems

22. All stages of qualification activities shall be contemplated, from the initial development of user requirement specifications to the end of the use of equipment, premises, utilities and other systems. The main stages as well as some proposed criteria (notwithstanding that they depend on project specifics and so may vary from project to project) that may be included into each of the described stages are given below.

User requirement specifications (URS)

23. The requirements to equipment, premises, utilities and other systems shall be defined by the user requirement specifications and (or) functional specifications. Quality components of major significance shall be considered at the early stages, while any risks shall be reduced to the acceptable level. The user requirement specifications shall be considered as the reference point of the validation lifecycle.

Design qualification (DQ)

24. The next component of qualification of equipment, premises, utilities and other systems is design qualification confirming and properly documenting the project's (design's) compliance with the requirements of these Rules. The user requirement specifications shall be verified during design qualification.

Factory acceptance testing (FAT) and (or) site acceptance testing (SAT)

25. Equipment (especially in case of implementation of new or combined technologies) may be assessed (if applicable) at the supplier's site prior to delivery.

26. Prior to installation (assembly), equipment shall be checked for compliance with user requirement specifications and/or functional specifications at the supplier's (manufacturer's) site if applicable.

27. Where applicable and reasonable, the documentation check and certain tests may be carried out within factory acceptance testing or at other stages without the need for re-testing at the customers site during installation

qualification and operation qualification, provided that the functionality cannot be affected as a result of transportation and assembly.

28. Factory acceptance testing may be supplemented with customer acceptance testing after the equipment is delivered to the manufacturing site.

Installation qualification (IQ)

29. Installation qualification shall be carried out for equipment, premises, utilities and other systems.

30. The installation qualification strategy may include the following, without limitations:

а) verification of the correct installation of components, equipment, instrumentation and auxiliary systems with regard to design drawings and specifications;

б) verification of the correct installation with regard to predefined criteria;

в) collection and completeness check of operation and maintenance guidelines provided by suppliers;

г) calibration of instruments;

д) verification of structural materials.

Operation qualification (OQ)

31. The operation qualification stage usually follows the installation qualification; however, depending on the equipment complexity, this stage may be combined with installation qualification (IOQ).

32. The operation qualification stage may include the following, without limitations:

the tests developed on the basis of the knowledge about the manufacturing process, systems and equipment to ensure the system's

operation according to design;

the tests aimed at confirmation of higher and lower operation limits and (or) "worst case" conditions.

33. Successful completion of the operation qualification stage allows for the approval of the following:

the final revision of standard operation procedures;

the cleaning procedure;

the operator training requirements;

the equipment maintenance requirements.

Performance qualification (PQ)

34. Performance qualification usually follows the successful completion of installation qualification and operation qualification. However, in some cases it may be combined with operation qualification or manufacturing process validation.

35. The performance qualification stage may include the following, without limitations:

а) the tests using production materials qualified as substitutes (equivalent materials) or model products with confirmed equivalent behavior at the common manufacturing conditions and the "worst case" batch size. The sampling frequency used to confirm the manufacturing process control shall be justified.

б) the tests shall cover the operating range of the manufacturing process, except for the cases when the operating range has been properly documented at the development stages.

4. Re-qualification

36. Equipment, premises, utilities and other systems shall be assessed with acceptable frequency in order to confirm their controllability.

37. If re-qualification is required and carried out with certain frequency, this frequency shall be justified and the assessment criteria shall be determined. In addition, the possibility of minor changes over time shall be assessed.

5. Manufacturing process validation

General information

38. The requirements and principles described in this section shall apply to the manufacturing of all dosage forms of all pharmaceuticals. They cover initial validation of new manufacturing processes, subsequent validation of modified processes, transfers between manufacturing sites and continuous verification of processes. This implies the full-scale product development process ensuring successful manufacturing process validation.

39. The requirements and principles described in this section shall be used together with the Guidelines on Validation of Manufacturing Processes of Pharmaceuticals for Human Use (Annex to Recommendation No. 19 of the Eurasian Economic Commission's Board dated September 26, 2017).

40. The Guidelines specified in Paragraph 39 shall apply only to the description of the information to be submitted to the regulatory bodies. The requirements of the Manufacturing Process Validation Rules cover the entire manufacturing process lifecycle.

41. This approach shall be used to connect the products and the development of the process for its manufacturing. This ensures that the

industrial manufacturing process validation and process maintenance remain controllable during the routine industrial manufacturing.

42. Manufacturing processes can be developed using a conventional approach or a continuous verification approach. However, regardless of the approach being used, the stability of the manufacturing process shall be confirmed and the product's stable quality shall be ensured prior to its release to the market. The manufacturing processes developed using the conventional approach are subject to prospective validation (if possible, prior to the product certification (market launch)). Retrospective validation is not considered an acceptable approach.

43. Manufacturing process validation for new products shall cover all manufacturing sites and dosage forms intended for the market. The selection of the extreme options (bracketing) may be justified for new products on the basis of extensive knowledge about the manufacturing process obtained during the product development, in combination with an acceptable continuous verification program.

44. In case of manufacturing process validation for the product transferred from one manufacturing site to another (or within one site), the number of validation batches may be reduced using the extreme option approach (bracketing). The product information shall be available, including the data from previous validation. The extreme option approach (bracketing) also may apply to different dosages, batch sizes and packaging sizes (types) if justified.

45. In case of the transfer of previously manufactured products ("legacy products") to the site, the manufacturing process and controls shall comply with the data of the drug master file and the effective registration requirements for the relevant group of pharmaceuticals. If necessary, such transfer shall be accompanied by changes in the drug master file.

46. Manufacturing process validation shall establish whether all quality indicators and manufacturing process parameters considered important for ensuring the validated status and acceptable quality of the products can be successively adhered to during the manufacturing process. The rationale for determining certain manufacturing process parameters and quality indicators to be critical or non-critical shall be clearly documented taking into account the results of quality risk assessment activities.

47. The batches produced for manufacturing process validation shall usually be of the same size as the planned commercial-scale batches. The use of other validation batch sizes shall be justified by validation documents or determined with reference to other sections of the Rules.

48. The premises, systems, utilities and equipment used for manufacturing process validation shall be qualified. The test procedures shall be validated according to their intended use.

49. Manufacturing sites for any products, regardless of the approach being used, shall be provided with knowledge about the manufacturing process, obtained at the development stage or from other sources (if there is no other rationale) and further used as a basis for validation activities.

50. Manufacturing staff and development service or transfer staff may be involved in the production of validation batches. The batches shall be manufactured by trained staff according to the Rules with the use of approved documentation. The manufacturing staff is supposed to participate in the production of validation batches for further understanding of the production process specifics.

51. The suppliers of critical and packaging materials shall be qualified prior to the production of validation batches. Otherwise the rationale shall be provided based on the use of the quality risk management principles.

52. The availability of the knowledge underlying the manufacturing processes is crucial to provide the rationale for the design parameter space (if applicable), as well as for development of any mathematical models used to confirm the manufacturing process control strategy.

53. If validation batches are going to be marketed, this shall be determined beforehand. Their manufacturing conditions shall fully comply with the requirement of the Rules, the validation acceptance criteria, the continuous production process verification (is applicable), as well as with the data specified in the master file or in the approval for clinical studies.

54. The manufacturing processes for pharmaceuticals used in clinical studies shall be validated in accordance with Annex No. 13 to the Rules.

Accompanying validation

55. Under exceptional circumstances, when there is a positive risk-to-benefit ratio for a patient, even unfinished validation program may be accepted prior to the launch of routine production, and accompanying validation may be used. The decision on accompanying validation shall be justified, properly documented in the validation master plan, and approved by authorized staff members.

56. The decision on accompanying validation shall be based on the proper rationale for homogeneity of the corresponding validation batch and its compliance with certain acceptance criteria. All results and conclusions shall be properly documented and made available for authorized persons before the batch is certified.

Conventional approach to validation

57. According to the traditional approach, a certain number of finished product batches is manufactured under routine conditions to confirm the reproducibility of the manufacturing process.

58. The number of manufactured series and the number of taken samples shall be based on the quality risk management principles, ensuring the establishment of normal trend and variation ranges, as well as providing sufficient data for assessment. The number of series required to confirm that the process ensures stable manufacturing of high-quality products shall be determined and justified.

59. The manufacturing of at least three successive product batches under routine conditions is usually considered as acceptable for manufacturing process validation, unless otherwise is specified by Paragraph 58 of this Annex. Another number of batches may be justified taking into account the use of standard manufacturing procedures and similar processes or products existing in the factory. In addition to the initial validation using three product batches, there may be the need for data obtained from the subsequent batches as part of continuous product verification.

60. The manufacturing process validation protocol shall be prepared to determine the critical process parameters, critical quality attributes (CQA) and related acceptance criteria that shall be based on the development process data or properly documented knowledge about the process.

61. Manufacturing process validation protocols shall include the following information, without limitations:

а) brief description of the manufacturing process and reference to the batch production and packaging records;

б) staff functions and obligations;

в) brief overview of the critical quality parameters to be examined;

г) brief overview of the critical parameters of the manufacturing process, and related limits;

д) brief overview of other (non-critical) indicators and parameters to be examined or monitored during validation (to be justified);

е) the list of used equipment and systems (including measuring, monitoring and recording equipment) together with calibration data;

ж) the list of analytical techniques and information about their validation (if applicable);

з) proposed in-process control measures with acceptance criteria, as well as the rationale for each selected in-process control measure;

и) additional testing (with acceptance criteria);

к) sampling plan and its rationale;

л) methods for registration and assessment of the results;

м) batch production and certification process (if applicable).

Continuous process verification

62. Continuous process verification may be used as an alternative to the conventional process validation approach for the products developed using the "quality by design" approach (when the designed routine manufacturing process has been scientifically proven to ensure high confidence in the product quality).

63. The method for continuous process verification shall be determined. A scientifically justified control strategy for the required parameters of supplied materials, critical quality indicators and critical manufacturing process parameters shall be determined to confirm the product sales strategy. The control strategy shall also be assessed on the regular basis. Useful tools for this purpose include the process analytical technology (PAT) and multi-

dimensional statistical control. The manufacturer shall determine and justify the number of series required to demonstrate a high degree of confidence that the process ensures stable manufacturing of high-quality products.

64. The general principles described in pp. 38-54 of this Annex shall also still apply to continuous process verification.

Hybrid approach

65. A hybrid of the conventional approach and continuous process verification may be used when there is a considerable amount of knowledge and understanding of the product and the manufacturing process, based on the manufacturing experience and historical data on the product batches.

66. This approach may also be used for any validation activities after applying changes or during continuous process verification, even if the conventional approach has been initially applied for the product.

Continuous manufacturing process verification during the lifecycle

67. Paragraphs 67-71 of this Annex shall apply to the three described approaches to manufacturing process validation (conventional, continuous and hybrid approach).

68. Manufacturers shall perform product quality monitoring to guarantee its controllable condition during the entire lifecycle with the assessment of the relevant manufacturing process trends.

69. The scope and frequency of the continuous process verification shall be periodically assessed. They may be changed at any moment of the product lifecycle based on the current understanding of the manufacturing process, as well as on the suitability of continuous manufacturing process verification.

70. Continuous verification of the manufacturing process shall be performed in accordance with the approved protocol or equal document. The relevant report form shall also be developed for proper documentation of the obtained results. If necessary, the manufacturer shall use statistical tools to confirm the conclusions on variability and opportunities of the manufacturing process, as well as to guarantee that the controllable condition is maintained.

71. Continuous verification of the manufacturing process shall be used during the product's entire lifecycle in order to maintain the validated status of the manufactured product (to be specified in the quality overview). The manufacturer shall also consider the subsequent implementation of additional changes and assess the need for any additional activities (e. g. extended sampling).

6. Transportation verification

72. Finished drug products, pharmaceuticals for clinical studies, unpackaged products and drug samples shall be transported from manufacturing sites under the conditions specified in drug master files and specifications, according to approved labeling or conditions justified by the manufacturer.

73. Although transportation verification may represent a problem due to a large number of different factors, the transportation routes shall be clearly described. Seasonal changes and other changing factors shall also be considered during transportation verification.

74. Quality risk assessment shall be performed to determine how the transportation process is affected by changing factors other than those controlled or monitored (e. g., transportation delays, data recording failures, adding liquid nitrogen, product sensitivity, and other related factors).

75. Since environmental conditions are subject to change during transportation, the manufacturer shall ensure continuous monitoring and recording of any critical environmental conditions the products may be exposed to, unless otherwise is justified.

7. Packaging validation

76. The change of equipment process parameters, especially those of primary packaging equipment, may significantly affect the integrity and proper functioning of packaging (e. g., blisters, pouches, and sterile components), so the equipment used for primary and secondary packaging of finished and unpackaged products shall be qualified.

77. Primary packaging equipment shall be qualified at the maximum and minimum values established for critical process parameters, such as temperature, equipment operation speed, adhesion (sealing) strength, or any other factors.

8. Utilities qualification

78. The quality of steam, water, air, other gases, etc., shall be confirmed after installation using the qualification stages described in Section 3 of this Annex.

79. Duration and scope of qualification shall reflect any seasonal changes if such changes affect the qualified object, as well as the intended use of the utility system.

80. Quality risk assessment shall be performed in order to prevent accidents in case of a potential direct (e. g., heating, ventilation and air conditioning systems) or indirect (e. g., heat exchangers) contact with the product.

9. Analytical procedure validation

81. All analytical procedures used for qualification, validation or cleaning validation shall be validated with regard to detection limits and assay limits (if necessary), as prescribed in Chapter 6 of the Rules.

82. In case of microbiological testing of the product, the test technique shall be validated to confirm that the product does not show anti-microbial properties.

83. In case of microbiological control of clean room surfaces, the control technique shall be validated to confirm the anti-microbial properties of cleaning agents and disinfectants.

10. Cleaning validation

84. Cleaning validation shall be performed in order to confirm the effectiveness of the cleaning procedure for all equipment contacting the product. Model substances may be used if the proper scientific rationale is available. If equipment of the same type is used, the manufacturer may select specific equipment items to perform cleaning validation if the proper rationale is available.

85. Visual cleanliness check is an important acceptance criterion for cleaning validation; however, it shall not be applied as a single one. Additional cleaning and additional testing until the compliance with acceptance criteria is reached are not considered an acceptable approach.

86. The cleaning validation program may require some time to be implemented; thus, validation with cleaning verification after each product batch may be required for some types of products, such as drugs intended for clinical studies. Verification shall provide sufficient information to confirm equipment cleanliness and further suitability.

87. Validation shall take into account the level of cleaning process automation. If the automated cleaning process is used, the manufacturer shall validate the operation range of parameters for utilities and cleaning equipment.

88. All cleaning processes shall be assessed to detect changing factors that may affect the cleaning procedure and its effectiveness, such as staff members, level of detail in the procedures (e. g., number of rinsing procedures), etc. If such factors are detected, the "worst case" conditions shall be utilized for cleaning validation.

89. The transfer limits for product residues shall be based on the toxicological assessment envisaged by the Guidelines on Permissible Limits of Human Exposure for Identification of Risks during Pharmaceutical Manufacturing in General Purpose Production (Process) Lines, approved by Decision No. 1 of the Eurasian Economic Commission's Board dated January 14, 2020. The rationale for selected limit values shall be properly documented within the risk assessment procedure, including references to the data sources used. The limits shall be established to confirm elimination of any used detergents. Acceptance criteria shall also take into account possible cumulative effects if the process flow chart includes several equipment units.

90. Therapeutic macromolecules and peptides are subject to degradation and denaturation when exposed to pH extremes and/or heat, and may become pharmacologically inactive. Therefore, toxicological assessment may be inapplicable under these circumstances.

91. If specific testing of the product residues is unavailable, other informative parameters (e. g., total organic carbon or electric conductivity) may be controlled.

92. The cleaning validation protocols shall be developed taking into account the risks of microbiological and endotoxin contamination.

93. Equipment storage time after the end of manufacturing before cleaning and the time between equipment cleaning and usage shall be taken into account to determine storage times for clean and contaminated equipment.

94. If manufacturing is conducted in campaigns, the manufacturer shall assess its cleaning capacity at the end of a campaign, while the maximum campaign duration shall be used as a basis for cleaning validation.

95. If cleaning validation is based on the "worst case" product approach, the manufacturer shall scientifically justify the selection of the "worst case" product and assess the new product's impact on the "worst case" selection. The "worst case" product selection may take into account various criteria, including solubility, easiness of cleaning, toxicity and activity.

96. Cleaning validation protocols shall describe or contain references to sampling points and the rationale for their selection, as well as determine the acceptance criteria.

97. Sampling shall be performed by taking washings from surfaces and (or) samples of liquid after rinsing, or by other methods depending on the equipment type. The choice of the sampling materials and methods shall not affect the obtained results. The manufacturer shall demonstrate the ability to extract substances from all materials of the equipment contacting the product, while using all methods provided for sampling.

98. To confirm that the cleaning method is validated, the cleaning procedure shall be carried out a relevant number of times (to be determined on the basis of risk assessment) and comply with acceptance criteria.

99. If the cleaning process is ineffective or unsuitable for some types of equipment, the manufacturer shall use special equipment or any other relevant measures for each product type, as prescribed in Section 3 and Section 5, Part I of the Rules.

100. If equipment is cleaned manually, it is especially important that the cleaning effectiveness is confirmed with justified frequency.

11. Change management

101. The change management process is an important component of the knowledge management process and shall be performed within the pharmaceutical quality system.

102. The documented procedures shall exist to determine the nature of activities to be performed in case of proposals for planned changes of raw materials, product components, process, equipment, premises, product lists, manufacturing processes or testing techniques, batch sizes, design parameter space or any other changes that take place during the product lifecycle and can affect product quality or process reproducibility.

103. If the design space concept is used, its changes shall be assessed in comparison with the master file data, and the need for the relevant regulatory activities shall be evaluated.

104. Planned changes shall be assessed using the quality risk management process, in particular, to determine a potential impact on the product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance, as well as any other systems for prevention of unpredicted consequences and planning of necessary activities for process validation, verification or re-qualification.

105. The changes shall be sanctioned and approved by responsible persons or the corresponding staff members according to the pharmaceutical quality system.

106. The confirmatory information (e. g., document copies) shall be assessed in order to determine the impact of the change before it is implemented.

107. Where applicable, the effectiveness of the change shall be subsequently assessed in order to confirm its successful implementation.

Terms and definitions

108. For the purposes hereof, the concepts having the following meanings shall be used:

"cleaning validation" shall mean a documented proof that the approved cleaning procedure will reproducibly ensure that, after the equipment cleaning, the amount of the residues of the previous product manufactured in this equipment, or the detergent used for the equipment cleaning, will be lower than the scientifically justified maximum permissible transfer level;

"cleaning verification" shall mean collection of evidence by means of chemical testing after every batch or campaign to confirm that the amount of the residues of the previous products or detergents after cleaning is lower than the scientifically justified maximum permissible transfer level;

"bracketing" shall mean the validation approach based on scientific and quality knowledge and on performance of the validation studies using the pre-determined and justified extreme values of certain factors, including drug dosage, batch size, and (or) package size. Thus, validation of all intermediate values is confirmed by validation of the extreme factor values only. This approach may be applied to a drug dosage range if the dosages are identical or very close in composition, e. g. for a line of tablets with different weights determined by press force, prepared from similar initial granulates, or a line of capsules prepared by filling the shells of different sizes with the different volumes of the drug product having the same composition. The bracketing approach may also be used in case of different package sizes or different filling volumes for the same container;

"quality by design" shall mean a systemic approach beginning from pre-determined objectives and focusing on product and process understanding, as well as on process control. It is based on scientific data and quality risk management principles;

"change control" shall mean a formalized system used by representatives of the corresponding fields of activities to check proposed or actual changes potentially affecting the validation status of premises, systems, equipment or processes. Its purpose is to determine the need to maintain and properly document the system's validated status;

"critical process parameter" shall mean a process parameter affecting critical quality attributes in case of its variability and being subject to monitoring and control in order to ensure the required quality;

"critical quality attribute" shall mean a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution range to ensure the required product quality;

"model products" shall mean materials having basically the same physical and, if necessary, chemical properties (such as viscosity, particle size, pH, etc.) as the validated product;

"worst case" is a condition or a set of conditions including upper and lower limit values of process parameters and related factors (within standard operation procedures) representing the highest probability of product or process noncompliance compared to ideal conditions. Such conditions do not necessarily lead to product or process noncompliance;

"continuous process verification" shall mean an alternative approach to process validation when the production process functioning is assessed and monitored on a continuous basis;

"prospective validation" shall mean validation carried out prior to the start of the serial manufacturing of the product intended for the market;

"continuous process verification (subsequent process verification)" shall mean a properly documented proof that the process remains controllable during the commercial production;

"accompanying validation" shall mean validation carried out under exceptional circumstances with the relevant rationale from the viewpoint of the patient benefit, during which the validation protocol is executed simultaneously with the release of the validation batches;

"user requirement specifications (URS)" shall mean a set of the owner's and the user's requirements, as well as specifications required and sufficient to create an acceptable project for intended use of the system;

"conventional approach" shall mean a product development approach ensuring reproducibility with the use of specified values and operation ranges of parameters.

Other terms used in these Requirements shall be applied in their meanings defined by the Rules of Good Manufacturing Practice approved by Decision No. 77 of the Eurasian Economic Commission's Council dated November 3, 2016.