ANNEX

to Decision of the Eurasian
Economic Commission's Council
No. _____ dated _____
____, 20___

**A M E N D M E N T S**
**to Decision No. 83 of the Eurasian Economic Commission's Council dated November 3, 2016**

1. Update Paragraph 1 with the following indent:

"Rules for Conducting Pharmaceutical Inspections for Compliance with Requirements of the Good Clinical Practice Rules."

2.Add the Rules for Conducting Pharmaceutical Inspections for Compliance with Requirements of the Good Clinical Practice Rules.

APPROVED

by Decision No. _____ of the
Eurasian Economic Commission's
Council,
dated _____ ____

# RULES
# for Conducting Pharmaceutical Inspections for Compliance with Requirements of the Good Clinical Practice Rules

## I. General Provisions

1. These Rules establish a common procedure for pharmaceutical inspections by the Pharmaceutical Inspectorate aimed at verifying Compliance with Requirements of the Good Clinical Practice Rules of the Eurasian Economic Union, approved by Decision No. 79 of the Eurasian Economic Commission's Council dated November 3, 2016 (hereinafter referred to as the inspection, Clinical Practice Rules, respectively).

2. The inspection shall be conducted to ensure compliance of clinical trials with the Clinical Practice Rules, including protection of the rights and well-being of trial subjects, quality and adequacy of data obtained in a clinical trial, as well as ethical aspects.

3. For the purposes of these Rules, the term 'inspection' shall apply to any activities carried out by a pharmaceutical inspectorate (on-site, remote and documentary inspections and verifications).

4. Inspectors are entitled to inspect clinical trial sites, documents, facilities, records, including documents of individual subjects, quality assurance measures, data, as well as other data sources and entities identified

in clinical trial documents as those authorized to perform specific trial procedures.

5. An inspection involves reviewing documents, infrastructure, records, quality assurance agreements, and any other data sources that are deemed by the authorized authority to be related to the clinical trial and that may be located at the clinical site, the Sponsor's and/or contract research organization's facilities, or in other organizations requiring inspection. If an inspection of clinical sites, laboratories or other facilities involved in a clinical trial is not required, documentary inspections are allowed by the decision of the authorized authority pursuant to the risk-based approach.

6. At the discretion of the pharmaceutical inspectorate, pharmaceutical inspections may be conducted by means of remote communication (e.g. by audio or video conference) in the following cases:

(a) A risk of occurrence, occurrence and elimination of an emergency and/or occurrence of a risk of spread of epidemic diseases that pose a danger to other people, diseases or injuries resulting from exposure to adverse chemical, biological, or radiation factors;

(b) Any force majeure circumstances or occurrence of the other circumstances independent of the Parties, which pose a threat to the life and health of the inspectors (e.g., for political, medical, or other reasons);

(c) At the discretion of the pharmaceutical inspectorate, sticking to a risk-based approach.

7. In their activities, the inspection team shall be guided by the developed and implemented Pharmaceutical Inspectorate Quality System of the Member States of the Eurasian Economic Union (hereinafter referred to as the Member States, the Union), in accordance with the General Requirements to the Pharmaceutical Inspectorate Quality System of the Member States of the Eurasian Economic Union approved by Decision

No. 82 of the Eurasian Economic Commission's Council dated November 3, 2016 (hereinafter referred to as the General Requirements to the Quality System), relevant approved procedures, which define the planning, arranging and conducting pharmaceutical inspections. The inspectorate quality system should have an organizational structure, clear processes and procedures (including standard operating procedures) to be followed by inspectors in fulfilling their tasks, clearly defined official duties and responsibilities of inspectors, continuous training requirements, and sufficient resources and mechanisms to eliminate nonconformities.

8. To ensure the protection of confidential information, in particular personal data of trial subjects, relating to their health, and commercially sensitive information, inspectors and experts involved in inspections shall comply with appropriate standards of confidentiality and applicable requirements of the legislation of the Member States and acts of the Union bodies (including international agreements). When processing personal data, inspectors and experts involved in inspections shall comply with the legislation of the Member States or third countries concerning personal data protection.

9. During inspections, inspectors should take into account the application of a risk-based approach to the planning and conduct of clinical trials.

10. These Rules shall apply to the following inspections, which cover:

clinical trials conducted in the Union, including sites associated with such trials but located in third countries;

clinical trials as specified in the Clinical Trial Application submitted in the Union;

clinical trials conducted in third countries and specified in applications for marketing authorization for medicinal products in the Union.

11. Inspections shall take place in the following cases:

before, during, and at the end of the clinical trial;

as part of the expert examination of applications for obtaining a marketing authorization for a medicinal product;

as follow-up action after obtaining marketing authorization of a medicinal product.

12. Inspections can be unscheduled and scheduled. Scheduled inspections shall be carried out according to the pharmaceutical inspectorate schedule, including within three years after marketing authorization of the medicinal product in accordance with the Rules for Marketing Authorization and Expert Examination of Medicinal Products for Human Use approved by Decision No. 78 of the Eurasian Economic Commission's Council dated November 3, 2016 (hereinafter referred to as the Rules for Marketing Authorization and Expert Examination). Inspection scheduling is allowed to be carried out in accordance with risk management principles.

## II. Qualification, training and experience of inspectors

13. Inspectors should have higher professional education in medicine, pharmacy, pharmacology, toxicology or other related fields consistent with the principles of Good Clinical Practice.

14. Inspectors should obtain appropriate training, including experience in participating in inspections. Their training needs to maintain or improve their skills should be routinely assessed by the pharmaceutical inspectorate's quality assurance service in accordance with the requirements of the Inspectorate's quality system.

15. Inspectors should be familiar with the principles and processes applied in the development of medicinal products and clinical trials, as well

as with the provisions of acts of the Union bodies and legislation of the Member States in the field of circulation of medicinal products.

16. Inspectors should be able to make professional judgements on the compliance of the entity under inspection with the acts of the Union bodies and the legislation of the Member States in the field of circulation of medicinal products. They are required to be able to assess the quality and integrity of data as well as the ethical aspects of clinical trials.

17. Inspectors should be familiar with the procedures and technical methods for documenting and handling clinical data, as well as with arrangements and regulation of health care systems in the Member States concerned and, if applicable, in third countries, where the trial is conducted.

18. The level of education and qualifications of inspectors should enable them to carry out risk assessments for:

safety of trial subjects;

the validity and quality of the data obtained.

19. Inspectors should be aware of applicable privacy and personal data protection regulations.

20. The pharmaceutical inspectorate of the Member State shall maintain documents concerning the qualifications, experience and training of each inspector, pursuant to the General Requirements for the Quality System.

## III. Observance of measures to avoid conflict of interests

21. Inspectors involved in the inspection shall not be under any influence that could affect their impartiality or judgement. No conflict of interests is allowed for inspectors. They should be independent of the inspection applicant and/or other inspection entities (including the Sponsor, investigators involved in the clinical trial, clinical trial funders, and any other party involved in the conduct of the clinical trial).

22. The candidacy of an inspection team member may be rejected if there is information about any potential conflict of interests.

23. Prior to an inspection, each inspector shall sign a declaration stating that they have no conflict of interest in conducting that inspection.

## IV. Inspection procedures

### Subject matter of the inspection

24. Inspectors should verify compliance with the approved clinical trial protocol, including the protection of the rights and well-being of trial subjects, the quality and adequacy of the data obtained in the clinical trial, compliance with the principles of Good Clinical Practice, including ethical aspects and the provisions of the legislation of the Member States.

### Procedures established by the Member States

25. The pharmaceutical inspectorates of the Member States shall have established inspection procedures for at least the following:

Engaging experts to fulfil certain duties if additional specialized knowledge is required within the inspection framework;

Arranging inspections on the territory of third countries;

Verifying compliance with the Clinical Practice Rules, including measures to control the trial arrangement procedures and the conditions for planning, conducting, monitoring, and documenting clinical trial data, as well as follow-up action such as verifying the root cause analysis in case of substantial non-compliance with the Clinical Practice Rules, and monitoring the Sponsor's corrective and preventive actions.

26. The pharmaceutical inspectorate of the Member State shall define the duties and responsibilities of the invited experts.

## Interaction of the Authorized Authorities (Expert Organizations) of the Member States

27. The authorized authorities (expert organizations) of the Member States shall collaborate to develop and improve generally accepted standards of inspections for compliance with the Clinical Practice Rules. Such interaction may take the form of joint inspections, harmonized processes and procedures, as well as exchange of experience and training of inspectors.

28. The Eurasian Economic Commission (hereinafter referred to as the Commission) should post on the Commission's official website in the information and telecommunications network "Internet" all the recommendations and guidelines on inspection standards developed jointly with authorized authorities (pharmaceutical inspectorates) of the Member States.

29. By March 31 of the reporting year, the pharmaceutical inspectorates of the Member States shall submit to the Commission information on the scheduled inspections in the reporting year and the inspections carried out in the previous year. The Commission shall post on its official website in the information and telecommunication network "Internet" the information submitted by the pharmaceutical inspectorates within 10 calendar days after receipt of the information to assist the authorized authorities (pharmaceutical inspectorates) of the Member States in the most efficient use of inspection resources in planning their inspections.

30. The authorized authority of a Member State shall be entitled to request the assistance from the authorized authority of another Member State on inspection issues.

Authority of inspectors

31. Inspections shall be carried out by inspectors appointed in accordance with the legislation of the Member State. Within the framework of each inspection, the pharmaceutical inspectorate of the Member State shall be entitled to appoint inspection teams and appropriately qualified experts to accompany the inspectors.

32. Inspectors are entitled to inspect clinical trial sites, laboratories and other premises, documents, facilities, records, including individual subject documents, quality assurance measures, trial data, and other sources and organizations considered by the authorized authority to be relevant to a clinical trial.

33. During the inspection, inspectors are entitled to have the access right to clinical trial sites, other trial-related premises and trial data, including individual subject documents.

34. Inspectors are entitled to copy documents, as well as photograph premises and equipment with the list of copied and photographed objects being handed over to the inspected entity.

35. Inspectors shall be entitled to interview a representative or employee of the entity under inspection, as well as representatives and employees of any party involved in the clinical trial, to obtain explanations regarding the subject matter and purpose of the inspection, and to record their responses in documentary form.

36. The authorized authority of the Member States shall accept the results of inspections carried out by the inspectorates of other Member States.

37. If there is disagreement between the authorized authorities of the Member States on the results of a pharmaceutical inspection, the authorized authorities of the Member States shall notify the Expert Committee on

Medicinal Products. After consultation with the Member States, the Expert Committee may initiate a joint inspection by the pharmaceutical inspectorates of the Member States.

38. The pharmaceutical inspectorate of the Member State shall appoint a sufficient number of inspectors to ensure effective verification of compliance of the clinical trial with Good Clinical Practice, as well as timely submission of inspection results. The inspection team shall include at least two pharmaceutical inspectors.

Confidentiality

39. Inspectors appointed to the inspection team and experts participating in the inspection shall ensure the confidentiality of information, documents they have gained access to during the inspection, and the inspection results.

Adopting a decision on the inspection assignment

40. Before scheduling an inspection, the pharmaceutical inspectorate shall evaluate the information available on the Commission's website or the Member States' inspection databases to determine the purpose, scope and extent of the inspection. When formulating the decision to conduct an inspection, the pharmaceutical inspectorate shall decide on the inspection scope, sites or other entities to be inspected, and the members of the inspection team.

41. The pharmaceutical inspectorate shall identify the contact person of the Applicant and/or the entity under inspection and notify the Applicant and/or the inspected entity of the inspection in writing and request (if necessary) additional documents or information (in accordance with Annex No. 1 to these Rules).

42. An inspection may be ordered by the authorized authority of the Member State within the framework of the expert evaluation of an application for obtaining marketing authorization of a medicinal product based on risk assessment and submitted documents as well as data in the marketing authorization application. In this case, the decision to order an inspection shall be communicated to the Applicant or the authorized person to initiate the inspection.

Analysis of documents and information

43. The information and documents required to prepare for and conduct the inspection should be identified, obtained and evaluated. The information required for the inspection may be obtained from the decision of the authorized authority (expert organization) to order an inspection, marketing authorization application, reference documents, scientific guidelines, as well as data obtained in accordance with the legislation of the Member States, standard operating procedures (SOPs), results of previous inspections, international and interstate standards (ISO, GOST), requirements of the legislation of the Member States, and additional documents requested from the Applicant, Sponsor or inspected entity, etc.

44. The list of documents to be used for pre-inspection analyses is given in Annex No. 2 to these Rules.

45. The reasons for the inspection should be assessed based on relevant documents and information. The results of such analysis, which were the ground for the inspection, shall be included in the program of inspection for compliance with the Clinical Practice Rules in the form given in Annex No. 3 to these Rules (hereinafter referred to as the inspection program).

46. The Sponsor or Applicant shall hand over to the inspection team the documents requested by them for inspection planning no later than 30 working days after receipt of the written request from the inspection team.

47. Upon review of the documentation, the inspection team members may conclude to invite an inspector and/or an expert with appropriate qualifications. Information on the formal approval and composition of the inspection team shall be contained in the inspection file, which shall be kept up to date.

## Inspection program

48. The inspection team shall prepare an inspection program to assist with respect to the entity under inspection. Different levels of detail are allowed in inspection programs. The decision to assign scheduled inspections may require less detail than unscheduled inspections of specific trials or inspected subjects.

49. The inspection program is a concise overview in nature, and defines the relevant aspects of the clinical trial subject and the scope to be covered during the inspection of the selected inspected entity. It will be based on the decision of the authorized authority to order the inspection and the results of the documentation review.

50. The inspection program shall contain:

timing of inspections it the site and/or other inspection entities;

timing of the report preparation (if applicable).

51. The inspection team shall be formed based on the relevant order of the head of the pharmaceutical inspectorate, and include the employees of the inspectorate in accordance with the procedures established by the quality system of the pharmaceutical inspectorate.

52. When trainees are included in the inspection team, their status shall be indicated in the order on the inspection team establishment.

53. The lead inspector and inspection team members should pre-evaluate documents and other available information related to the inspected activity.

54. If necessary, the authorized authorities (expert organizations) are entitled to request additional documents from the Applicant in order to prepare for the inspection.

55. The lead inspector shall coordinate the preparatory activities and ensure the program development, preparation of checklists, or other forms of working records as stipulated in the quality system of the pharmaceutical inspectorate no later than 20 working days before the day of the inspection.

56. To ensure that the inspection objectives are achieved, the lead inspector shall be entitled to amend the inspection program during the inspection.

## Communication about the inspection

57. The inspection team shall inform the Applicant or Sponsor and/or the inspected entity about the inspection and the responsible personnel of the inspected entity in accordance with the procedures implemented in the pharmaceutical inspectorate of the Member State.

58. The inspection dates of the selected inspected entity shall also be communicated to the site, Applicant or Sponsor in accordance with the timing of the inspection plan.

59. If an unscheduled inspection within the framework of the marketing authorization of a medicinal product is ordered by the authorized authority, the inspection timing shall not exceed 40 working days from the date of submission of an application for inspection by the Applicant.

60. The Sponsor or Applicant is authorized to request a pre-inspection meeting to discuss the inspection scope (especially to clarify aspects of the inspection scope). The pharmaceutical inspectorate will arrange such a meeting if required, provided this does not increase the inspection lead time.

61. Depending on the type of inspection, type of trial, therapeutic area of use of the medicinal product and type of medicinal product, location of the inspection, number of selected inspected subjects, etc., the scope of training may differ between inspections.

## Responsibilities of the Lead Inspector

62. The Lead Inspector shall:

interact with the parties involved in conducting the inspection and deciding on its assignment;

verify the location (geolocation) of the inspection entity, coordinate, arrange and determine the composition of the inspection team;

agree the inspection program;

prepare, update, ensure the inspection file quality and protection, and maintain the archives in accordance with the approved procedures;

initiate inspection preparations upon formal receipt by the Applicant of a copy of the decision to order the inspection in accordance with the established procedures;

propose and set timing for inspection activities (preparation and conduct of inspection, preparation of reporting);

request the required documentation and information to be submitted to the inspection team;

evaluate the quality and sufficiency of the documentation and information provided;

immediately communicate the submitted documentation and information to the inspection team;

decide whether more information is needed from the parties involved in the inspection;

carry out inspections in accordance with the approved documents (of the pharmaceutical inspectorate and the applicant) and the requirements of the legislation of the Member States;

verify compliance with the inspection timing throughout all inspection stages;

verify compliance with confidentiality requirements;

ensure that the inspection documents are up-to-date and kept protected;

ensure that all relevant reference documents are available and that important local features or differences of the entity under inspection are communicated to the inspection team.

Kick-off meeting

63. When conducting an inspection, the Lead Inspector shall hold a kick-off meeting with representatives of the inspected entity, at which the Lead Inspector shall introduce the members of the inspection team, become acquainted themselves with the authorized persons of the inspected entity and clarify their tasks and responsibilities, including allocation of duties and functions in the conduct of the trial, and, if applicable, clarify the regulatory requirements for conducting the inspection, declare the objectives and scope of the inspection, specify the inspection program, inspection plan and schedule (including confirmation of the time and date of the closing meeting and any interim meetings), make a statement of confidentiality, and answer any questions from the inspected entity.

64. The purpose of the kick-off meeting is also to:

communicate any internal organizational practices, the Member State practices or other procedures affecting the implementation of quality systems or compliance of the inspected entity with the Clinical Practice Rules;

provide a summary of the methods and procedures used to conduct the inspection;

certify that the resources, documents, electronic systems and facilities required by the inspectors are available.

Performance of inspection and data collection

65. The main inspection activities should be specified in the inspection program. To ensure that the inspection objectives are met, the program may be amended during the inspection.

66. By reviewing relevant direct access documents, interviews and observations of activities, equipment and conditions in the inspected areas, sufficient information should be collected to fulfil the inspection purpose. Personal information (full names) and positions of the persons being interviewed or present during inspection meetings and data on the inspected entity should be documented.

67. If access to records or systems is denied, or access to inspected areas is denied, such denials should be documented and included in the inspection findings.

68. During the inspection, members of the inspection team, in accordance with the inspection program, shall visually examine the inspected facilities, familiarize themselves with documentation and records, and interview the responsible persons of the inspected entity. The information obtained shall be entered on a checklist or other forms of working records.

69. Any findings not recorded during the inspection cannot be further used in categorizing nonconformities.

70. At the end of each inspection day, the Lead Inspector shall hold a meeting with the inspection team members to discuss preliminary findings, which, if required, shall be further discussed with the responsible persons of the inspected entity. In case of any disagreements, the inspection team members shall answer questions from representatives of the inspected entity.

71. The information provided by the responsible persons of the inspected entity on the elimination of any findings made during the inspection shall be taken into account by the inspection team and listed in the inspection report as nonconformities with a note about their elimination during the inspection.

72. The description of specific inspection elements for each type of inspected entity is given in Annexes Nos. 4 to 8 to these Rules.

73. For each specific inspection element, the way in which the data are obtained, collected, reported, analyzed, amended and archived (if applicable) should be verified.

## Findings (nonconformities) during inspection and inspection protocols

74. Any findings and nonconformities identified during the inspection should be documented. If justified, copies of records containing inconsistencies or exemplifying a nonconformity should be made.

75. At the end of the inspection, inspectors should reevaluate all findings to determine which will be reported as nonconformities. In that case, inspectors should ensure that nonconformities are documented in a clear concise manner and supported by objective evidence.

76. The reported nonconformities should be accompanied by references to the specific requirements of the standards or other related documents

inspected for compliance. The findings not considered as nonconformities are acceptable to be documented as comments.

77. If provided for in the quality system of the inspectorate, the inspection findings shall be summarized in the protocol (or its equivalent) prepared by the inspectors at the end of the inspection.

78. During the inspection, the inspection team members shall fill out checklists or other forms of working records and submit them to the Lead Inspector.

79. Any nonconformities identified during the inspection of a clinical trial are categorized as follows:

Critical nonconformities, i.e. any nonconformities that adversely affect the quality, integrity and adequacy of the clinical trial data or have a negative impact on the rights, safety and well-being of trial subjects Nonconformities classified as major imply unacceptable data quality, including manipulation and deliberate data contamination, and lack of source documentation. This type of nonconformity is unacceptable.

Major nonconformities, i.e. nonconformities that cannot be categorized as critical, but are capable of adversely affecting the quality and integrity and/or adequacy of the clinical trial data, or are capable of adversely affecting the rights, safety and well-being of the trial subjects;

Minor (other) nonconformities, i.e. nonconformities that do not affect the quality and integrity of the data and do not adversely affect the rights, safety and well-being of trial subjects. The identification of such nonconformities indicates the need to improve the conditions, procedures, and processes for conducting clinical trials, while many such violations cumulatively can be classified as major.

## Closing meeting with inspected persons

80. The main purpose of this meeting is to present the identified nonconformities and the inspectors' comments to the inspected persons and the relevant management of the inspected entity (if necessary) to ensure that the inspection results are adequately understood by all participants and that there is no misunderstanding on the part of both the inspectors and the inspected persons. The issues to be addressed by the inspected person should be highlighted, including any additional documents that may require subsequent presentation to the inspection team.

81. During such a meeting, inspectors should report on the submission and review of inspection reports (including deadlines for responses) and any additional scheduled inspections (e.g., associated trial sites).

82. At the closing meeting with the responsible persons of the inspected entity, the preliminary results of the inspection are announced with a discussion of the identified nonconformities.

## Inspection report and follow-up action based on inspection results

83. The result of the inspection is the preparation of an inspection report containing a conclusion about the compliance or non-compliance of the clinical trial with Good Clinical Practice.

84. Based on the results of identified nonconformities, the report contains recommendations to the Authorized Authority and makes a conclusion about the compliance or non-compliance of the clinical trial with the Clinical Practice Rules.

85. If required, the report clarifies the part of the clinical trial, the data of which may be regarded as invalid.

86. The report shall contain an assessment of compliance with national and applicable Union regulations and principles of Good Clinical Practice. The validity and adequacy of the data recorded or presented shall be assessed within the context of the inspection scope. Any major or critical deviations should be specified.

87. These elements should be described in the report, and nonconformities classified as minor (or "other"), major, or critical. Each nonconformity shall contain a reference to the applicable regulatory and legal requirement with respect to which non-compliance has been established.

88. If applicable, an assessment of the effects of nonconformities should be included and a general conclusion should be made on the trial compliance or non-compliance with the Clinical Practice Rules, as well as the effect of the identified nonconformities on the quality of the data obtained and the results of the trial.

89. For inspections related to marketing authorization of a medicinal product or completed trials, a recommendation should be made as to whether the quality of the data submitted allows them to be used when reviewing the application for marketing authorization of the medicinal product. At the same time, the report shall indicate nonconformities that can directly affect the assessment of the benefit-risk ratio of the medicinal product, and that do not have such a direct effect, but were identified as systemic deficiencies (for example, standard operating procedures and processes), that is, related to the Clinical Practice Rules.

90. Some inspections may be entirely focused on subject safety or rights during the active phase of the trial and may not address issues related to marketing authorization of a medicinal product.

91. The Lead Inspector shall draw up a report using the form presented in Annex No. 8 to these Rules within 20 working days from the date of inspection completion and submit it to the inspected entity.

92. The inspected entity submits their responses to the received inspection report no later than 20 working days from the date of receipt of the report. If critical and/or major nonconformities were identified during the inspection, the response is accompanied by a corrective and preventive action (CAPA) plan and a report on its completion or data indicating that the identified nonconformities have been eliminated (if applicable). For minor nonconformities, no CAPA plan will be submitted unless otherwise specified in the inspection report.

93. The responses and CAPA plan (if applicable) provided by the inspected entity shall be included as an annex entitled “Responses of the Inspected Entity” to the inspection report. If additional materials are attached to the responses, the Lead Inspector shall determine whether they should be included in the “Responses of the Inspected Entity” annex. The inspection report should not be updated or amended based on the review of the responses. The final conclusion will be given in the “Evaluation of the responses from the inspected entity” annex to the inspection report, based on the responses provided and the CAPA plan (if applicable).

94. No later than 15 working days, the inspection team shall assess the information contained in the response, followed by preparation of a summary of the submitted response assessment, with an indication of the final number of critical, major and minor nonconformities and development of a final statement. The summary shall be presented as an annex entitled "Evaluation of the responses from the inspected entity" to the inspection report.

95. If the inspected entity fails to respond to the inspection report within 20 working days, the Lead Inspector shall indicate this fact in the

annex "Evaluation of the responses from the inspected entity" to the inspection report.

96. The annex entitled "Evaluation of the responses from the inspected entity" to the inspection report shall contain recommendations for further action, including an assessment of the need for re-inspection to evaluate the elimination of nonconformities.

97. The final report shall be considered the inspection report with annexes entitled "Responses from the inspected entity" and "Evaluation of the responses from the inspected entity."

98. If the inspection is conducted by a team of inspectors, the Lead Inspector is responsible for preparing the report. The final report shall be prepared in 3 copies. The final report should be agreed and signed by all inspectors and inspection team experts involved.

99. One copy of the report shall be submitted to the Applicant or Sponsor or inspected entity (with a cover letter) not later than 3 working days from the date of its signing, the second copy shall be addressed to the authorized authority of the Member State, which grants marketing authorization of medicinal products, and the third copy shall remain deposited in the archives of the pharmaceutical inspectorate.

100. The Pharmaceutical Inspectorate shall ensure the security and confidentiality of information contained in the inspection documents.

101. The authorized authority of the Member State shall post on its official website in the information-telecommunication network "Internet" the information concerning the inspections performed, indicating their results.

102. Upon request, the inspection report can also be made available to other regulatory authorities, ethics committee in accordance with the legislation of the Member States.

## V. Conducting inspections as part of the procedures for obtaining the marketing authorization of a medicinal product

103. The grounds for considering the need for inspection shall be the assessment of the data contained in the Marketing Authorization Application for the medicinal product, taking into account possible risks and compliance with paragraphs 27, 36 to 39 of the Rules for Marketing Authorization and Expert Examination of Medicinal Products for Human Use approved by Decision No. 78 of the Eurasian Economic Commission's Council dated November 3, 2016 (hereinafter referred to the Rules for Marketing Authorization and Expert Examination).

104. Any inspections during procedures for obtaining the marketing authorization of a medicinal product are carried out on a scheduled and unscheduled basis.

105. Scheduled inspections for compliance with Good Clinical Practice are carried out in the first three years after obtaining the marketing authorization of a medicinal product.

106. Unscheduled inspections are carried out by decision of the authorized authority of the Member State within the framework of the procedures for obtaining the marketing authorization of a medicinal product.

107. When assessing the data in the marketing authorization application within the framework of the procedure for obtaining marketing authorization of medicinal products, the authorized authority (expert organization) of the reference Member State, which performs an expert examination of the medicinal product within not more than 60 working days from the date of receipt of the application for marketing authorization of the medicinal product, makes a decision on the need (or lack thereof) to conduct an inspection in accordance with paragraphs 36 to 39 of the Rules for Marketing Authorization and Expert Examination.

108. In the decision adopted, the authorized authority of the Member State shall formulate the grounds and scope of the inspection, the site and, if applicable, the list of relevant issues to be addressed during the inspection.

109. When selecting the pharmaceutical inspectorate of the Member State carrying out inspections for compliance with Good Clinical Practice, the following principles (in order of priority) shall be taken into account:

а) the inspecting authority is located in the reference Member State that performs the expert examination of the marketing authorization application during the procedure for granting the marketing authorization of a medicinal product;

б) the inspecting authority is located in the country in which the clinical trial that is the subject of the inspection has been (is being) conducted;

в) the inspecting authority is located in the Member State concerned specified in the application for marketing authorization of the medicinal product;

г) the inspecting authority is located in other Member State.

110. The experts, who carry out the evaluation of the marketing authorization application within the framework of the procedure for obtaining marketing authorization of medicinal products, and the inspectors should discuss the scope of the inspection and the selection of inspected sites and agree between them, as guided by Section IV of these Rules. To save limited resources and time, when formulating their opinion, inspectors may rely on available inspection reports prepared by third-country inspectors (if any).

111. The inspection report shall include information on compliance or non-compliance of the clinical trial with the Clinical Practice Rules and contain a recommendation that the clinical trial data can be used when reviewing an application for marketing authorization of a medicinal product

or that the clinical trial data cannot be used for evaluation of an application for marketing authorization of a medicinal product.

112. The inspection report shall be submitted to the applicant for inspection. The findings of the inspection report shall be placed in a common database of the Union, which is accessible to all Member States (if any), in accordance with paragraph 101 of these Rules

113. If the inspection outcome is unfavorable (contains critical non-conformities and a finding of non-compliance of the clinical trial with the Clinical Practice Rules or a finding that the data from that clinical trial cannot be used to evaluate the application for marketing authorization of the medicinal product), the reference Member State, in consultation with the Member States concerned (if any), should provide for the measures required in the context of the application for marketing authorization of that medicinal product or an already approved marketing authorization of that medicinal product (e.g., imposition of an additional commitment, refusal to approve the medicinal product).

114. Scheduled and unscheduled inspections for compliance with the Clinical Practice Rules based on documents and information submitted by the Applicant within the framework of marketing authorization, taking into account the assessment of possible risks, shall be carried out at the expense of the Applicant and/or the Marketing Authorization Holder.

Unscheduled inspections

115. The decision on the need for an unscheduled inspection is made by the authorized authority of the reference Member State based on a comprehensive assessment of the relevant factors specified in paragraphs 38 and/or 39 of the Rules for Marketing Authorization and Expert Examination:

(a) The lack of information on the approval of the clinical trial by the Independent Ethics Committee;

(b) Identification of violations when obtaining informed consent or information to be provided to the trial subjects;

(c) Issues related to the administrative structure of the clinical trial (lack or ambiguity of the information);

(d) Significant deviations from the approved trial protocol that are not documented;

(e) No or insufficient information on the measurement of the efficacy and/or safety parameters (concerning sampling, identification, processing of the clinical trial samples, assay conditions) in the clinical trial protocol and report;

(f) Availability of information on exclusion of the data of trial subjects from the statistical analysis without any justification;

(g) Identification of facts that raise doubts about the reliability of the data presented in the marketing authorization application regarding the clinical trial of the medicinal product (unjustified or unclear differences of efficacy and safety endpoints in the protocol and the clinical trial report; inconsistent, inaccurate or incomplete recording of data, protocol amendments are not reflected in other documents of the clinical trial; a large number of missing values that may affect the statistical power of the trial);

(h) Implausible or inappropriate clinical data (conflicting data compared to known data of other trials, low reporting rate of serious adverse reactions and/or implausible data in favor of the investigational product compared to the results obtained by other investigators or in other trials, medically or biologically controversial (implausible or conflicting) results between trials or trial sites);

(i) Critical dependence (substantiation of the efficacy and safety of the drug, as well as its benefit-risk ratio) on the results of a single trial or trials with a small subject population only;

(j) the medicinal product is intended for use in a large population (for example, vaccines or other medicinal products intended for simultaneous use by large populations);

(k) High potential for ethical concerns (participation in the trial of vulnerable populations: children, persons with cognitive impairment, subjects with co-morbidities lacking alternative therapy, institutionalized subjects, etc., in accordance with requirements of the Clinical Practice Rules);

(l) the clinical trial is conducted in a site located in a geographical region where the requirements for clinical trials are inferior to those established in the Union;

(m) information from the authorized authorities of third countries regarding concerns with the trial site or the Sponsor’s compliance with Good Clinical Practice.

116. The decision on the need to conduct an unscheduled inspection with respect to the results of bioequivalence studies shall be made by the authorized authority based on a comprehensive assessment of the following factors:

(a) presentation of unreasonably homogeneous (heterogeneous) data of a bioequivalence trial;

(b) the number of missing/outlying values is inconsistent compared to the estimated values for this active substance or method of measurement;

(c) implausibility (inconsistency) of clinical, statistical, or analytical data;

(d) the presence of conflicting trial data in respect of the pharmacokinetic parameters or the within-subject (between-subject) variability.

117. If a decision is made to initiate an unscheduled pharmaceutical inspection, the authorized authority of the reference Member State communicates to the Applicant a decision on the need to arrange an inspection of the clinical trial (specifying the inspection subject and the grounds for initiating the inspection, taking into account the risk assessment and references to the acts of the Union authorities in the field of circulation of medicinal products) within 5 working days after such decision is made.

118. It is the Applicant's responsibility to notify the Sponsor and other parties involved in the conduct of the clinical trial of the upcoming inspection.

119. Upon receipt of a decision/request on the need to conduct an unscheduled inspection as part of the marketing authorization procedure, the Applicant for obtaining a marketing authorization of a medicinal product or the Marketing Authorization Holder (or their authorized person) shall submit an application to the authorized authority of the reference Member State concerning performance of an inspection, provided the decision/request in question is received no later than 15 working days, and also provide additional information if a corresponding request is received.

120. Upon receipt of an application for an inspection, the pharmaceutical inspectorate shall agree with the Applicant on the timing of the inspection within 20 working days, include the inspection in the inspection schedule and communicate to the authorized authority about the planned date of the inspection completion.

In case of a documented decision that it is not feasible for the pharmaceutical inspectorate of the reference Member State to carry out an

inspection, the Applicant shall be entitled to apply to the pharmaceutical inspectorate of another Member State for an inspection.

121. An unscheduled inspection shall be carried out in time, within a period not exceeding the period of examination of the Marketing Authorization Application.

122. If a decision is made to conduct an inspection for compliance with the Clinical Practice Rules, the expert examination of the medicinal product shall not be suspended.

123. However, if before the preparation of the assessment report on the safety, efficacy, and quality (not later than 100 working days from the date of expert examination start), the authorized authority (expert organization) of the reference Member State does not receive information on the inspection report, it shall send a request to the Applicant to submit the results of the inspection. From the date of sending this request to the Applicant, the examination is suspended.

124. To provide a response to the said request the Applicant shall have no more than 180 working days, which will not be included in the period of the expert examination.

125. If the Applicant fails to submit the inspection results requested by the authorized authority within the established term, the expert examination of the medicinal product shall be terminated. The authorized authority shall notify the Applicant and, if applicable, the authorized authorities of the Member States of the decision within 14 working days from the date of such decision in written and/or electronic form.

126. The final expert report is prepared taking into account the inspection results.

Scheduled inspections

127. Scheduled inspections in relation to clinical trials, including bioequivalence studies, are carried out by decision of the authorized authority of the reference Member State based on the documents and information submitted by the Applicant as part of marketing authorization of a medicinal product, taking into account an assessment of possible risks in the first three years after marketing authorization in accordance with paragraphs 36 to 39 of the Rules for Marketing Authorization and Expert Examination of Medicinal Products for Human Use, or the inspection plan (if applicable).

128. The need to conduct a scheduled inspection within 3 years after marketing authorization of a medicinal product is established by the authorized authority of the reference Member State as a post-approval requirement in accordance with the provisions of Section VII.I of the Rules for Marketing Authorization and Expert Examination of Medicinal Products for Human Use.

129. The Applicant initiates a scheduled inspection after marketing authorization of a medicinal product within the period determined by the established requirements in accordance with the expert report, but no later than 3 years after marketing authorization.

The results of the scheduled inspection are submitted by the Applicant to the authorized authority of the reference Member State in accordance with the Rules for Marketing Authorization and Expert Examination of Medicinal Products for Human Use.

130. The inspection report received is taken into account by the authorized authority of the reference Member State when revising the assessment report on the safety, efficacy, and quality of the medicinal

product, as well as when establishing additional measures or restrictions on the circulation of this medicinal product.

Annex No. 1

to the Rules for Conducting Inspections
for Compliance with Requirements of the
Good Clinical Practice Rules

(form)

**DECISION (REQUEST)**
**on the Assignment of a Pharmaceutical Inspection for Compliance with Good Clinical Practice by the Authorized Authority of the Member State of the Eurasian Economic Union**

| | | |
|---|---|---|
| Name of the authorized authority | Full name of the contact person or expert | Telephone, fax, e-mail |
| | | |
| Name of the Sponsor or company | | |
| Name of the medicinal product | | |
| Name of the active substance | | |
| Name of the clinical trial | Select one of the key pivotal trials based on the expert evaluation report, marketing authorization application | |
| Protocol number | | |
| Number of the clinical trial within the Eurasian Economic Union (if available) | | |
| Trial phase | | |
| Type of marketing authorization procedure | For example, mutual recognition procedure or decentralized procedure | |
| Member State(s) concerned | | |
| Therapeutic indications | | |
| Trial dates | | |
| Other information | | |

List of inspected subjects

| Name of the organization | Address of the inspected Sponsor or Contract Research Organization, clinical or laboratory site | Contact person or investigator | Telephone and e-mail |
|---|---|---|---|

| | | | |
|---|---|---|---|
| | | | |
| | | | |

| | |
|---|---|
| List of issues to be assessed during the inspection | |
| 1 | |
| 2 | |
| 3 | |
| 4 | |
| Other relevant information | |
| For example, about the results of a previous inspection of the site or Sponsor | |
| Scheduled inspection period | |
| Planned date for the inspection report submission | |
| Name | |
| Signature | |
| Date | |

Annex No. 2

to the Rules for Conducting Inspections
for Compliance with Requirements of
the Good Clinical Practice Rules

**DOCUMENTS AND INFORMATION**
**that can be used for**
**evaluation before the inspection**

1. Inspection-related documents:

(a) a request or decision to assign an inspection;

(b) inspection procedures;

(c) expert reports (if applicable);

(d) list of questions, answers (if applicable);

(e) a blank inspection report form.

2. An overview of trial conduct:

(a) reports, final report;

(b) availability of an equivalent or extended trial protocol.

3. Inspected trial sites:

(a) curriculum vitae and qualifications of the Investigator and Co-Investigator;

(b) information about the involved or selected sites (including, for example, pharmacies, clinical departments, X-ray departments, magnetic resonance imaging and computed tomography departments, ultrasound departments, EchoECG departments (functional diagnostics), contract research organizations).

4. Laboratories:

(a) local and central;

(b) type of laboratories participating in the trial;

(c) type of examinations and tests, special equipment and procedures.

5. The Sponsor:

(a) responsibilities established by agreements with involved contract research organizations;

(b) the clinical trial protocol, amendments thereto, investigator's brochure;

(c) the case report form;

(d) the participant information sheet and informed consent;

(e) a printout of (parts of) the clinical database;

(f) quality management (quality control and quality assurance);

(g) the Sponsor's standard operating procedures related to the inspection scope;

(h) monitoring procedures and monitoring reports;

(i) a monitoring plan;

(j) a data management plan;

(k) a statistical analysis plan;

(l) information about the electronic systems used in the trial;

(m) risk assessment and mitigation plan, if applicable.

6. Medicinal products in the trial:

(a) information on compliance with Good Manufacturing Practice, such as a certificate;

(b) information about the production site;

(c) labeling;

(d) blinding procedures;

(e) the patient randomization list and procedures (e.g., IVRS);

(f) quality documents;

(g) the batch release certificate.

7. Ethical aspects:

(a) the participant information sheet and informed consent form;

(b) the patient recruitment process;

(c) insurance documents;

(d) safety information or IB updates;

(e) the Ethics committee favorable opinion or approval, if applicable.

8. Applicable regulations and guidelines:

(a) applicable legal requirements of the acts of the authorities of the Eurasian Economic Union and the legislation of the Member States of the Eurasian Economic Union;

(b) a notification or approval of the trial;

(c) a decision (request) of the authorized authority to assign an inspection;

(d) insurance;

(e) medicinal products used in the trial: labeling, storage, destruction;

(f) reporting of serious adverse events.

9. Tabular lists of individual patient data

Annex No. 3

to the Rules for Conducting Inspections for Compliance with Requirements of the Good Clinical Practice Rules

**(form)**

**PROGRAM**
**of Conducting Inspections for Compliance with Requirements of the Good Clinical Practice Rules**

_____

(name of the trial site)

1. Grounds for the inspection _____

2. Objectives of the inspection _____

3. Scope of the inspection _____

4. Date and place of the inspection _____

5. Inspection team members _____

6. Allocation of responsibilities between inspection team members _____

7. Inspection schedule

| Start date and time <*> | Inspection stage ** |
|---|---|
| | 1. Kick-off meeting |
| | 2. Familiarization with the documentation of the quality management system |
| | 3. Familiarization with the employee records |
| | 4. Familiarization with the inspected entity (premises, equipment) |
| | 5. Familiarization with the clinical trial documentation |
| | 6. Familiarization with source documents on the conducted and ongoing clinical trials |
| | 7. Inspection team meeting |
| | 8. Closing meeting |

<*> Can be completed at the kick-off meeting.
<**> Sample content is provided.

| 8. | Inspection subject (section of the Rules of Good Clinical Practice of the Eurasian Economic Union) <*> (if applicable) | Full name of the inspector (expert) | Full name of the authorized person of the inspected entity <**> |
|---|---|---|---|
| CLINICAL TRIAL SITE | | | |
| 1. | Kick-off meeting | | |
| 2 | Legal and administrative aspects | | |
| 3. | Organizational issues | | |
| | 3.1. Organization and personnel | | |
| | 3.2. Facilities and equipment | | |
| | 3.3. Biosample handling | | |
| | 3.4. Document management | | |
| | 3.5. Monitoring and audit | | |
| | 3.6. Use of computerized systems. | | |
| 4 | Informed consent of the trial subjects | | |
| 5 | Evaluation of the subject data | | |
| | 5.1. Eligibility of the subjects enrolled in the clinical trial based on the trial inclusion and exclusion criteria | | |
| | 5.2. Plan of trial subject visits | | |
| | 5.3. Efficacy and safety assessment data | | |
| | 5.4. Concomitant therapy and intercurrent disease | | |
| 6. | Handling of investigational medicinal product | | |
| 7 | Interim meetings | | |
| | 7.1 Inspection team meeting | | |
| | 7.2 Meeting with representatives of the inspected subject (overview of the preliminary results of each inspection day) | | |
| 8 | End of inspection | | |
| | 8.1 Inspection team meeting | | |
| | 8.2 Closing meeting Familiarization of the inspected entity representatives with the | | |

| | | | |
|---|---|---|---|
| | preliminary results of the inspection | | |
| | Sponsor and/or Contract Research Organization (CRO) | | |
| 1. | Kick-off meeting | | |
| 2. | Inspection of the Sponsor's or Contract Research Organization's quality systems | | |
| | 2.1. Organization and personnel | | |
| | 2.2. Facilities and equipment | | |
| | 2.3 Sponsor's and Contract Research Organization's standard operating procedures | | |
| 3. | Inspection of a specific clinical trial | | |
| | 3.1. Clinical trial conduct and termination | | |
| | 3.2 Monitoring | | |
| | 3.3 Investigational medicinal product | | |
| | 3.4 Safety and reporting of adverse events | | |
| | 3.5 Verification of data in case report forms | | |
| | 3.6. Data processing and clinical trial report | | |
| | 3.7. Recording and archiving of the clinical trial data | | |
| | 3.8. Audit | | |
| 4 | Interim meetings | | |
| | 4.1 Inspection team meeting | | |
| | 4.2 Meeting with representatives of the inspected organization (overview of the preliminary results of each inspection day) | | |
| 5 | End of inspection | | |
| | 5.1 Inspection team meeting | | |
| | 5.2 Closing meeting<br>Familiarization of the inspected entity representatives with the preliminary results of the inspection | | |

| | | | |
|---|---|---|---|
| CLINICAL LABORATORY | | | |
| 1. | Kick-off meeting | | |
| 2 | Legal and administrative aspects | | |
| 3. | Organizational aspects. Scope and delegated responsibilities | | |
| | 3.1. Organization and personnel | | |
| | 3.2. Premises, equipment, reagents | | |
| 4. | Protocol-specific aspects of work associated with the clinical trial | | |
| | 4.1. Biosample handling | | |

| | | | |
|---|---|---|---|
| | 4.2. Material and methods | | |
| 5. | Procedures for reporting laboratory results | | |
| | 5.1 Procedures for reporting and evaluating the results and data transfer | | |
| | 5.2 Notification systems for results that are unanticipated and/or major deviations from predetermined limits | | |
| | 5.3 Transfer of source data into trial findings | | |
| | 5.4 Traceability of the evaluation and confirmation of results by responsible personnel | | |
| | 5.5 Procedures for correcting and amending the results | | |
| | 5.6 Complaint handling and corrective actions | | |
| 6. | Quality assurance. Intralaboratory quality control results. Participation in external quality audit systems | | |
| 7 | Interim meetings | | |
| | 7.1 Inspection team meeting | | |
| | 7.2 Meeting with representatives of the inspected organization (overview of the preliminary results of each inspection day) | | |
| 8 | End of inspection | | |
| | 8.1 Inspection team meeting | | |
| | 8.2 Closing meeting. Familiarization of the inspected organization representatives with the preliminary results of the inspection | | |
| BIOANALYTICAL PART, PHARMACOKINETIC AND STATISTICAL ANALYSES OF BIOEQUIVALENCE STUDIES | | | |
| 1. | Kick-off meeting | | |
| 2. | Bioanalytical Part of bioequivalence studies | | |
| | 2.1. General site structure | | |
| | 2.2. Sample tracking | | |
| | 2.3. Sample analysis | | |
| 3. | Pharmacokinetic and statistical analyses | | |
| | 3.1. Pharmacokinetics | | |
| | 3.2. Statistical analysis | | |
| 4. | Interim meetings | | |
| | 4.1. Inspection team meeting | | |
| | 4.2 Meeting with representatives of the inspected organization (overview of the preliminary results of each inspection day) | | |
| 5. | End of inspection | | |
| | 5.1 Inspection team meeting | | |

| | | | |
|---|---|---|---|
| | 5.2 Closing meeting Familiarization of the inspected entity representatives with the preliminary results of the inspection | | |

<*> Sample content is provided.
<**> Filling out at the kick-off meeting is allowed.

9. Approximate deadline for submission of the inspection report (additional sheet).

Annex No. 4

to the Rules for Conducting Inspections for
Compliance with Requirements of the
Good Clinical Practice Rules

## Inspection of the clinical trial site

1. This annex contains a description of specific elements that may be verified at the trial site, but their selection will depend on the inspection scope and may be established by the inspection plan. When determining the documentation, including electronic documents, that shall be submitted and available for the inspection, it should be referred to the clinical trial authorization, the Rules of Good Clinical Practice of the Eurasian Economic Union, approved by Decision No. 79 of the Eurasian Economic Commission's Council dated November 3, 2016 (hereinafter referred to as the Clinical Practice Rules), the requirements of the legislation of the Member States of the Eurasian Economic Union (hereinafter referred to as the Member States, the Union) and the list of essential documents.

2. The purpose of the inspection is to establish compliance with the requirements for conducting a clinical trial. Inspectors shall verify compliance with the approved clinical trial protocol and its subsequent changes (amendments to the clinical trial protocol), reporting on trial safety and any other required approvals, notifications, exchange of information, compliance with Good Clinical Practice, statutory obligations and applicable requirements of the acts of the Union's authorities and legislation of the Member States.

3. For trial sites located on the territory of the Union, the clinical trial authorization granted by the authorized authority of the Member State and its

significant changes, as well as other notifications about the clinical trial and the exchange of information for their further verification in the trial site may be available through information systems of the authorized authorities of the Member States. A clinical trial authorization includes an ethical review by the ethics committee, which shall be carried out in accordance with the legislation of the Member State. In this regard, inspectors should check any Member State-specific conditions regarding the ethical evaluation set out in the decision, which may require further confirmation in the trial site.

4. For trial sites located in third countries, an ethical expert opinion may be required, separate from the clinical trial authorization, access to which shall be available in the trial site for verification.

5. In both cases, when checking a trial site in view of the expert examination by the Ethics Committee, the following aspects should be considered as appropriate:

(a) Determine whether there is an independent ethics committee (IEC) for a given site and check if there is a statement that it is arranged and operates in accordance with the Clinical Practice Rules, as well as in accordance with the applicable legislation of the Member State where the inspection is conducted. If applicable, check the accreditation or authorization of the Independent ethics committee by the authorized authorities of the State where the inspection is conducted and whether the independence and composition of the independent expert committee are consistent with the national requirements of the State where the inspection is conducted while inspections in third countries should take into account national requirements as appropriate;

(b) Verify that an approval or a favorable opinion from the Independent ethics committee (signed and dated) has been obtained before starting the trial and implementing any amendments to the clinical trial

protocol at the site, which clearly identifies the trial, the investigator, the documents reviewed and their versions. The same shall be verified in case of amendments to the clinical trial protocol and the adoption of any emergency safety measures, if applicable;

(c) Verify that the investigator and/or Sponsor has copies of all reports submitted to the Independent ethics committee, including initial submissions and approvals (favorable opinion), and reports of all actions or changes required for a preliminary approval or favorable opinion and other changes to applicable documents;

(d) Check whether annual reports have been submitted to the Independent ethics committee, if applicable.

6. Any other approval required to conduct the trial at the site and the fact that sufficient information about the trial has been provided to other involved parties at the site (head of the healthcare facility, pharmacy, etc.) should be verified. Documents of trial subjects' insurance and reimbursements should be verified.

## I. Assessment of organizational aspects

### 1. Evaluation of the trial conduct at the trial site

7. Inspectors should check the following elements:

(a) Organization and personnel:

organizational structure (trial site management and its organizational structure);

documents related to delegation of responsibilities by the Principal Investigator and acceptance by the trial team;

quality control (QC) and quality assurance (QA) systems, if available;

a system of standard operating procedures (SOP), if available;

emergency plans (for example, handling faulty equipment);

information about employees: curriculum vitae, qualifications, responsibilities, experience, professional training programs, documentation of professional training and retraining;

the number of clinical trials conducted and their nature;

the proportion of time devoted to clinical trial work.

(b) Agreements between the Sponsor (or the Contract Research Organization) and the investigator, between the Sponsor (or the Contract Research Organization) and the administration of the trial site, if applicable;

the qualifications and experience of the trial team in the clinical field under consideration;

documents describing the allocation of responsibilities and functions for conducting the trial;

compatibility of the Investigator and personnel workload with trial requirements;

arranging a site for clinical trial operations: organizational structure, GCP training, training on the trial under consideration, special equipment, special procedures;

the documented clinical trial authorization and a permit to supply an investigational medicinal product (IMP);

adherence to the trial schedule;

accurate and timely implementation of current versions of the trial protocol and amendments thereto, the informed consent form and its amendments;

the first visit of the first patient (enrollment or screening) and the last visit of the last patient;

(c) Facilities and equipment.

Inspectors shall verify the correct use, sufficiency and validation status of procedures and equipment used during the conduct of a clinical trial. If applicable, perform facility round checks (e.g., clinics, pharmacies, laboratory processing areas). The following elements are to be checked:

equipment used;

equipment maintenance, attendance and calibration;

the premises used to conduct the trial;

their compliance with the protocol and the characteristics of the inspected trial.

Annex No. 5 to these Rules shall apply to the inspection of a clinical laboratory or centralized laboratory;

(d) Biosample handling.

Inspectors should check the conditions and documentation for handling biosamples (if applicable):

sample collection (the person responsible for sample collection, dates and processing procedures, including labeling);

sample storage conditions prior to analysis or transportation;

sample transportation conditions;

interaction with the laboratory, actions of the inspected subject in case of identification of nonconformities on the laboratory side;

receipt, evaluation and storage of sample results;

(e) Document management.

Inspectors should determine the availability of dated and signed general documentation and documents of trial subjects (if applicable), and the organization of archiving systems at the trial site (inspections in third countries should take into account the requirements of the legislation of those countries, as appropriate).

(f) Monitoring and audit.

Elements to be considered (if any):

the Sponsor's monitoring and follow-up: number of monitor visits to the clinical site, monitoring scope and dates of visits if requested by the Sponsor; actions required from the monitor, monitoring plan and standard operating procedures;

audit certificates (from the Sponsor's file);

(g) Use of computerized systems.

Computers may be specially designated to the trial and provided by the Sponsor. They may be site-specific and constitute a part of the site's standard equipment (medical records, online laboratory data, ECG recording, etc.).

## 2. Informed consent of trial subjects

8. Inspectors shall establish the fact that the informed consent of the subjects has been obtained in accordance with the conditions for granting the clinical trial authorization and the requirements of the legislation of the State where the inspection is conducted, as well as the requirements of the Union's authorities acts, by checking the relevant sample of trial subjects (patients) (including subjects or patients whose medical records have been inspected) or legal representatives of the subjects before they enter the trial. The assessment of obtaining the informed consent should include all patients whose medical records have been subject to inspection (with inspections in third countries taking into account the legal requirements of those countries as appropriate).

Elements to be considered:

(a) A signed and self-dated (by the trial subject and informed consent interviewer) consent form used and approved by the Independent ethics committee at the time subjects were enrolled in the trial;

(b) The information sheet actually used and approved by the Independent ethics committee to determine whether it contains all the elements required by the acts of the Union authorities and the legislation of the State in which the inspection is carried out;

(c) A procedure for issuing a copy of informed consent to the subject at the trial site;

(d) A consent to give access to medical records for regulatory authorities and other authorized persons;

(e) Fixing in the source document the process of obtaining initial informed consent and subsequent consent updates, including a child consent in pediatric trials and emergency consent, if applicable.

3. Review of trial subject data

9. Through source data verification, inspectors should check whether the Investigator's team has conducted the clinical trial in accordance with the approved protocol and protocol amendments. In source data verification, initial records should be evaluated, taking into account their structure, completeness and legibility. It should be assessed whether the corrections to the data recorded in the case report form comply with the requirements of the acts of the Union's authorities and the requirements of the legislation of the Member States (with inspections in third countries taking into account the requirements of the legislation of these countries, as appropriate), (signed and dated by the authorized person and containing a justification where necessary).

For multiple trial subjects (the sample may include the first and last patients enrolled, etc.), the following elements are to be checked:

Eligibility of the subjects enrolled in a clinical trial based on the trial inclusion and exclusion criteria.

Inspectors should determine whether subjects were enrolled in accordance with the approved clinical trial protocol and/or that violations of the protocol were documented and that these violations were described in the clinical trial report.

Elements to be considered:

(a) the subjects enrolled in the clinical trial, who did exist and participate in the clinical trial;

(b) participation of the subjects in the trial is documented in their medical records;

(c) the subjects enrolled in the trial met the inclusion criteria; also, there were no exclusion criteria specified in the clinical trial protocol.

## 4. Plan of trial subject visits

10. Inspectors shall determine whether the visit schedule for the trial subjects was observed as specified in the clinical trial protocol. This check includes a review of the dates of the trial visits to assess whether they were conducted on the correct dates.

## 5. Data on safety and efficacy of the medicinal product

11. Inspectors should verify that the efficacy and safety data recorded in the case report form are consistent with the source data obtained during the trial and that sufficient data management procedures were in place at that time. Endpoint data should be compared with source records, if warranted by the inspection scope.

Such verification also includes assessing the recording of adverse events reported in the site's records on the case report form and reporting them to the Sponsor, the Independent Ethics Committee and the authorized

bodies in accordance with the procedures established by the laws of the State in which the inspection is conducted.

During the review of safety data, cases of early termination of the intervention and subject dropout from the trial should be evaluated.

## 6. Concomitant therapy and intercurrent diseases

12. Inspectors should check whether work with concomitant therapy and intercurrent diseases was carried out in accordance with the clinical trial protocol and whether an appropriate entry about this was made to the case report form and source documents.

## 7. Handling investigational medicinal product and unapproved auxiliary medicinal product

13. Inspectors shall verify that all activities related to the investigational medicinal product are carried out in accordance with the clinical trial protocol and other trial documents.

Elements to be considered:

(a) Instructions for handling the investigational medicinal product and trial materials (if not included in the trial protocol or Investigator's brochure);

(b) Documentation on the transportation of investigational medicinal products, as well as trial materials. Date of receipt of the delivered investigational medicinal product and its quantity. This documentation should include batch numbers (check with the Sponsor for data consistency), expiration dates, and codes assigned to the investigational medicinal product and a trial subject;

(c) The appearance of the investigational medicinal product and the comparators used (if they are still at the site during the inspection).

(d) Documentation on the intervention prescribed, randomization, and unblinding of investigational drug codes;

(e) Accountability of the investigational and unapproved auxiliary medicinal products at the site (by the pharmacy or the Investigator):

Date of dispensing and quantity of the investigational medicinal product dispensed and returned, recipient identification data (subject or authorized person code). This documentation shall also contain batch numbers, expiration dates, and codes assigned to the investigational medicinal product and trial subject;

Documentation of relabeling of the investigational medicinal product (if applicable);

Return date and quantity of the investigational medicinal product returned to the Sponsor. Return Form: This documentation shall also contain batch numbers, expiration dates, and codes assigned to the investigational medicinal product and trial subject;

(f) Documentation of destruction of the investigational medicinal product (if destroyed at the site): dates of destruction and quantity of the investigational medicinal product destroyed. Documentation or certificate of destruction;

(g) Adherence (compliance) of the trial subjects;

(h) Other actions in accordance with the clinical trial protocol;

the suitability of the storage conditions and records thereof (refrigerator, freezer or controlled substances, etc.) should be checked;

the pharmacy or institution's specific standard operating procedures for such activities, if available, should be reviewed;

it should be checked whether controlled access to the investigational medicinal product has been ensured from receipt to return to the Sponsor for destruction or destruction at the trial site;

verification of the labeling for compliance with the applicable requirements of the Union's law and the legislation of the State where the inspection is conducted.

Inspectors shall verify that, where appropriate, the specified documents have been signed and dated by the responsible persons in accordance with the site's and/or the Sponsor's standard operating procedures and/or the applicable requirements of the Union's law and the legislation of the State where the inspection is conducted, concerning handling of investigational medicinal products.

Annex No. 5

to the Rules for Conducting Inspections for
Compliance with Requirements of the
Good Clinical Practice Rules

## Inspection of clinical laboratories

1. This annex applies to the inspection of clinical laboratories performing the analysis or evaluation of human biosamples collected during the clinical trial.

This annex provides a simple listing of the elements to be considered when inspecting clinical laboratories.

2. The following are the main aspects that need to be assessed during the inspection.

(a) General aspects:

baseline information:

scope and delegated responsibilities;

availability of an accreditation for the laboratory and an indication in the accreditation scope of this laboratory, relevant ISO and GOST for the types of activities or test methods, as well as the availability of GLP and GMP certificates. A laboratory accreditation status is not assessed and is not required for the analysis of clinical samples, but it may indicate the availability of a formal quality system;

fulfillment of accreditation requirements stipulated by the legislation of the State where the inspection is conducted (if required);

the relevance of accreditation in the context of clinical trial(s);

a proportion of work related to the analysis of samples from clinical trials;

(b) Organization and personnel:

organizational structure (facility management, scientific organizational structure, reporting lines in quality assurance (QA));

quality assurance and quality control systems, including internal audit programs;

a system of standard operating procedures (SOPs) appropriate to the work being undertaken, including relevant support systems;

resuming activities after emergencies and ensuring business continuity;

employees: qualifications, responsibilities (given in job descriptions and/or delegated), experience, availability, training and competency assessment programs, training logs, curriculum vitae;

(c) Contractual rights and obligations:

procedures, e.g. for agreements, clinical trial protocol, protocol amendments, source data definitions, reporting agreements;

the specification of methods and procedures;

access and availability for monitoring, audits and inspection;

data registration, processing and archiving;

security and protection of the confidentiality of trial subject data;

work standards (compliance with the documents of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, Clinical Practice Rules, applicable legislation of the State where the inspection is conducted);

reporting of serious deviations;

Informed consent requirements (if reviewed elsewhere): availability, withdrawal or correction of informed consent, notification of changes, coverage of sample analysis;

requirements for the urgent reporting of data concerning the safety of trial subjects and the protection of blinded data;

(d) Facilities and premises:

the adequacy and appropriateness of the premises ('fitness for purpose'), e.g. sufficient separation of work areas to prevent confusion, contamination or distortive interference;

ambient conditions such as temperature, air current and atmospheric pressure, microbiological contamination (in relevant cases);

security and safety (e.g. fire safety, flood defense and pest control);

(e) 'Fitness for purpose' (e.g. laboratory areas, archive, sample storage areas) with appropriate controls (access, fire safety, pest control). Instruments and equipment, materials, reagents:

the instruments are available, in good working condition and meet relevant specifications (calibration, validation, maintenance);

quality of general-use consumables, including tap water, analytical water, gases, etc.;

records of operation, maintenance and calibration of laboratory systems, supported by relevant risk assessments and justification to demonstrate fitness for purpose;

documents related to method validation;

the materials and reagents are prepared, labelled, documented and stored under appropriate conditions, respecting expiration dates. Reagent labels indicate their authenticity, source, concentration, and expiration dates;

the instruments and materials used do not significantly affect the samples;

a definition of source data and source documents, retrieval and archiving. Data generated by electronic systems, including recording, transfer, storage and archiving, recovery, inspection and reconstruction.

3. Trial-related aspects.

An inspection should also include consideration of all issues applicable to the clinical trial.

(a) Handling of samples:

preliminary evaluation:

samples obtained in a clinical trial from subjects, date and time (if relevant to the analysis), identification data, labeling, previous storage and transportation conditions, preparation, storage;

consideration of patient privacy issues in the labeling text (if applicable, for example, if the laboratory is located remotely from the site);

consideration of any blinding limitations;

documentation of acceptance (date and time), identification, condition, relabeling (barcoding) and storage of samples by an identifiable person;

confirmation by the analytical laboratory that the handling and transfer of samples prior to the analysis was in accordance with the requirements of the clinical trial protocol, that is, procedures for storage at the clinical site and transfer or transportation of samples to the laboratory;

documented procedures for accepting or rejecting (discarding) samples for analysis;

aliquoting;

transfer of samples for checking;

documented procedures to ensure traceability;

checking:

compliance with the clinical trial protocol and established validated analytical methods;

traceability and identification of samples and controls;

recording data, documenting of acceptance and issuing of results;

handling nonconformities, reanalysis and results in critical or alarming ranges;

supporting data such as equipment, storage conditions, etc.;

the competency, professional training and experience of the personnel;

recreating the lab's actions during the analysis;

post analysis procedures:

data management, statistical analysis and reporting;

long-term storage (if required), retrieval and destruction of samples;

(b) Material and methods:

material and methods in accordance with the specifications given in the clinical trial protocol or agreement, and/or required in accordance with the Pharmacopoeia of the Eurasian Economic Union, approved by Decision No. 100 of the Eurasian Economic Commission's Board dated August 11, 2020 or other applicable compendial standards;

validation status of methods, appropriate establishment of detection or quantitation limits, precision and accuracy, known biases and specific control measures;

4. Reporting laboratory results.

The clinical trial protocol or agreement may provide for different systems for reporting laboratory results, such as reporting of each sample analysis (for urgent consideration in the care of a trial subject) or in a pooled form (for use in a clinical trial report). The type of reporting system affects the procedures used by the laboratory and the procedures used during the inspection.

(a) Procedures for reporting and evaluating the results and data transfer;

(b) Notification systems for results that are unanticipated and/or major deviations from predetermined limits;

(c) Transfer of source data to the clinical trial report:

laboratory identification data;

unique identification data and location of the inspected entity;

the investigator's credentials;

date and time of sample collection, as well as time of their acceptance;

date and time of the clinical trial report review and release;

the source of the main type of the sample and any comments on its quality;

description of the analysis and its results;

the limit of detection, the uncertainty of each measurement, and the reference intervals (if applicable);

interpretation of results and other comments, where appropriate;

credentials of the person who prepares the report;

(d) Tracking the review and release of the report by responsible personnel;

(e) Procedures for correcting and making amendments to reports;

(f) Procedures for complaint handling and corrective actions.

5. Quality assurance

Adequacy of data reported by the Sponsor's quality control or quality assurance personnel and/or similar personnel at the Sponsor's side (audit certificate).

Annex No. 6

to the Rules for Conducting Inspections for
Compliance with Requirements of the
Good Clinical Practice Rules

## Inspection of the Sponsor and the Contract Research Organization

This annex summarizes the specific elements that are allowed to be checked at the premises of the Sponsor's or contract research organization (CRO) performing trial responsibilities on behalf of the Sponsor's.

There are two different approaches:

(a) a systemic inspection;

(b) an inspection of a specific clinical trial.

The selection of items to be inspected depends on the inspection scope and should be included in the inspection plan. During the inspection, a sufficient sample of data, documents, elements from individual trials should be checked to confirm the functional operation of the described process. If individual trials form a part of the decision to order an inspection, this sample will be drawn primarily from such trials.

If a risk-based approach is applied to the planning and conduct of clinical trials, inspectors should take this into account during inspections. Risk adaptations shall be clearly described and justified in terms of risk assessment and mitigation. The risk-based approaches used in the trial may influence the content of the trial master file in that some documents may be combined or missing, depending on the risk adaptations performed and in accordance with the risk assessment and mitigation plan.

## I. Inspection of Quality Systems of the Sponsor or Contract Research Organization

The purpose of the inspection is to assess the quality assurance and quality control systems implemented by the Sponsor or the Contract Research Organization to ensure that the clinical trials are conducted in a comprehensive way to provide for the rights and safety of the trial subjects, as well as the registration, processing, reporting and storage of data obtained in clinical trials, in accordance with the Protocol, the Rules of Good Clinical Practice of the Eurasian Economic Union approved by Decision No. 79 of the Eurasian Economic Commission's Council dated November 3, 2016 (hereinafter referred to as the Clinical Practice Rules), and applicable requirements of the legislation of the State where the inspection is conducted to assure their validity and reliability.

When inspecting the Sponsor's or Contract Research Organization's systems, the following elements should be considered:

### 1. Organization and personnel

Inspectors shall evaluate whether the Sponsor or Contract Research Organization has arranged the clinical trial activities well enough and has a sufficient number of appropriately qualified and trained personnel in each field.

To be checked:

(a) an organizational structure ensuring an identification of key personnel in each field;

(b) independence of the quality assurance unit;

(c) job descriptions, qualifications and training of personnel involved in any stage of the clinical trial process.

## 2. Facilities and equipment

Inspectors should identify and evaluate the facilities used in the trial (e.g., archiving facilities, storage of the investigational medicinal product), as well as the equipment used in the trial. Particular attention should be paid to computerized systems (hardware, software, communications, etc.) to assess their validation status and adequacy for the needs of the trial being inspected.

## 3. Sponsor's and Contract Research Organization's Standard Operating Procedures

Inspectors should evaluate the system of standard operating procedures and associated documents (for example, forms, templates and policies in a particular area of activity). Individual procedures should be reviewed to ensure they comply with standards of the Clinical Practice Rules and applicable operating regulations.

## Clinical trial conduct and termination

Inspectors should evaluate the procedures developed for the conduct and termination of clinical trials.

Review the procedures in terms of:

(a) Preparation of documents: format and content, as well as distribution of the clinical trial protocol and amendments thereto, informed consent documents, Investigator’s brochure, case report form and any other trial documents:

selection and training of investigators;

fulfilment of the requirements stipulated by the State where the inspection is conducted: obtaining an approval of the clinical trial protocol (or a favorable opinion) from the Independent ethics committee and the

required permits to conduct clinical trials, provided for by the requirements of the acts of the Union's authorities and the legislation of the State where the inspection is conducted.

## Monitoring

Inspectors should evaluate the clinical trial monitoring system. To determine whether the Sponsor's monitoring procedures provide for:

(a) description of the risk-based approach to monitoring (if applicable);

(b) Description of the logic of the selected monitoring strategy in the trial, specific monitoring plans: planning, frequency, depth and nature of monitoring activities (visits, data checks, etc.), monitoring responsibilities, etc.;

(c) Description of monitoring activities in trial sites and via a centralized procedure;

(d) Content, processing and follow-up of monitoring reports;

(e) The consent to give a direct access to the Sponsor's personnel (and their assigned representatives) and regulatory authorities to source documents, and observance of confidentiality of the trial subject data;

(f) A description of the training and monitoring process (e.g. joint monitoring visits, process for escalating identified issues, resourcing).

## Trial medicinal product

Inspectors shall determine the compliance of the Sponsor's procedures at different stages of the life cycle of the investigational medicinal product with the current requirements 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, and Good

Clinical Practice of the Eurasian Economic Union, approved by Decision No. 79 of the Eurasian Economic Commission's Council dated November 3, 2016, or equivalent requirements in accordance with the applicable legislation of the State where the inspection is conducted.

Determine whether these procedures establish requirements for:

(a) A risk-based approach to handling the investigational medicinal product (if applicable);

(b) The quality control of the investigational medicinal product;

(c) Manufacture, packaging and labeling of the investigational medicinal product;

(d) Storage and transportation of the investigational medicinal product;

(e) Supply, accounting, return and destruction of the investigational medicinal product;

(f) Randomization and unblinding of the investigational medicinal product code;

(g) Validation of the computerized systems used.

## Sample handling

The procedures established for handling of samples collected in clinical trials should be reviewed.

## Safety and reporting of identified adverse events

Inspectors should check procedures for evaluation and reporting findings that may adversely affect the safety of trial subjects and for reporting identified serious adverse events to regulatory authorities, investigators, and the independent ethics committee (if applicable).

Review the procedures concerning:

(a) A risk-based approach to reporting of safety information and identified adverse events (if applicable);

(b) Identification by the Investigator and/or Sponsor of adverse events, serious adverse events, serious unexpected adverse reactions;

(c) Urgent reporting of identified adverse reactions to the authorized authority, investigators and independent ethical committee (if applicable);

(d) Notification by investigators of identified serious adverse events;

(e) Processing information about identified serious adverse events reported by investigators;

(f) Updates of safety information and periodic safety update reports;

(g) Preparation, implementation and use of the Investigator's Brochure (IB) and Reference Safety Information (RSI), safety monitoring and profiling, handling information from the Independent Data Monitoring Committee (IDMC), if applicable;

(h) Validation of the computerized systems used.

## Non-compliance with requirements

Procedures for handling significant non-compliance with requirements in clinical trials should be reviewed (e.g., analysis and reporting of potential and actual serious deviations, including the logbook, decision rationale for each deviation, results and corrective and preventive action (CAPA) plans, outcomes).

## Data management and clinical trial report

The system established by the Sponsor or Contract Research Organization for handling data obtained during a clinical trial and reporting thereof in the clinical trial report should be evaluated.

Determine whether the procedures establish:

work procedure, analysis and data check procedures;

preparation of a clinical trial report in accordance with standards of the Clinical Practice Rules;

Validation of the computerized systems used;

introduction of a chronology of events log (for paper and computer systems).

## Document archiving

It should be verified that the system established by the Sponsor or Contract Research Organization ensures that the essential documents to be archived on the Sponsor and Contract Research Organization side (compliance of the trial master file with the Clinical Practice Rules) are available, complete and secure within the fixed time period. The contents of the trial master file are influenced by the risk-based approach applied to the trial.

Determine whether the procedures provide for:

(a) A system for archiving and retrieving documents. The storage system (regardless of the media used) shall ensure identification, search and retrieval of documents;

(b) Controlled access to archives and electronic systems.

## The Sponsor's audit and quality assurance system

It should be determined whether the Sponsor or Contract Research Organization has implemented a system for auditing its quality assurance system to evaluate its activities affecting clinical trials.

Determine whether the procedures entail:

(a) Audits of key processes of clinical trials, including monitoring, data management, safety data reporting, preparation of clinical trial reports, archiving and validation of computerized systems;

(b) Audits of contractors and subcontractors.

Inspectors should also review:

processes for communicating and evaluating audit findings, including the format of audit reports and the procedure for distributing thereof;

procedures describing actions in case of a critical and/or major nonconformity with standards of the Clinical Practice Rules;

a chronology of events log;

procedures for developing and implementing an audit program (plan);

risk-based quality management, if applicable.

## Delegation of responsibilities

The purpose is to review the procedure for contracting or subcontracting of the trial responsibilities. Inspectors should review procedures affecting:

(a) Pre-selection and continuous evaluation of a contractor and a subcontractor;

(b) Timely documentation of delegation of responsibilities;

(c) Oversight of any trial-related responsibilities and functions performed by contractors or subcontractors;

(d) Project management and general trial oversight, both internal and external;

(e) The availability of the approved documents confirming delegation should be checked.

3. Inspection specific to a clinical trial

The purpose of this type of inspection is to verify whether the trial has been conducted, data obtained, documented and reported in accordance with the clinical trial protocol, principles of the Clinical Practice Rules, applicable regulatory requirements and the Sponsor's procedures. The procedures and requirements applied during the trial should be reviewed and compared with the procedures and requirements applied during the inspection.

Trial-specific inspections are also conducted to address the issues listed in the inspection assignment.

During a trial-specific inspection, inspectors shall check all of the following stages, processes, and materials used in the clinical trial.

Clinical trial conduct and termination

The purpose is to verify that all legal and administrative aspects of the clinical trial have been completed.

Inspectors should review procedures affecting:

(a) Allocation of the Sponsor's responsibilities or functions. Oversight of any personal and trial responsibilities and trial-related functions performed by contractors or subcontractors;

(b) Information provided to investigators and/or specific training;

(c) Selection of investigators and agreements with them;

(d) Fulfilment of the requirements of the State where the inspection is carried out: an approval or favorable opinion of the independent ethics committee and the required authorizations;

(e) Submission and approval of amendments to the clinical trial protocol, assessment of urgent safety measures, assessment of serious violations, assessment of the analysis of the protocol deviations;

(f) Critical dates: an approval or favorable opinion of the Independent ethics committee, clinical trial authorization (if required), the trial starting date, the period of subject enrollment in the trial, closure of trial sites, and termination of the trial.

## Monitoring

The inspector should check:

(a) Description of the risk-based approach to monitoring, if applicable;

(b) A monitoring plan or standard operating procedures (availability, content and adherence);

(c) Frequency and scope of monitoring activities;

(d) Qualifications of the clinical monitors;

(e) Monitoring visit reports and review of reports by the Sponsor or Contract Research Organization;

(f) Central monitoring activities and evaluation of reports by the Sponsor or Contract Research Organization;

(g) Corrective actions initiated based on the results of monitoring visits.

## Trial medicinal product

Inspectors should review procedures affecting:

1. A risk-based approach to handling investigational medicinal products, if applicable;

(a) Manufacture, packaging, labeling and quality control of the investigational medicinal product;

(b) Supply, accounting, returns and destruction (the system of tracking the investigational medicinal product);

(c) Randomization of trial subjects and unblinding of the investigational medicinal product code;

(d) Blinding of the investigator and masking the medicinal product data;

(e) Transportation, including permit to supply the investigational medicinal product in accordance with the legislation of the State where the inspection is conducted;

(f) The condition of the delivered investigational medicinal product after receipt and during storage;

(g) Validation of the computerized systems used.

## Safety and reporting of identified adverse events

Inspectors should review procedures affecting:

(a) A risk-based approach to safety and reporting of identified adverse events, if applicable;

(b) Notification, follow-up and reporting of identified serious adverse events and information on other non-serious adverse events requiring urgent reporting in accordance with the clinical trial protocol;

(c) Updates to safety information and safety signals;

(d) Preparation, implementation and use of the Investigator's Brochure (IB) and Reference Safety Information, active monitoring or profiling of safety data, handling information from the Independent Data Monitoring Committee, if applicable;

(e) Validation of the computerized systems used.

## Verification of data in case report forms

A predetermined number of case report forms should be checked to ensure:

(a) Adherence to the clinical trial protocol and the accuracy, completeness, legibility and timeliness of data receipt;

(b) Amendments to the case report forms;

(c) Consistency of the dates of the first patient and last patient enrollment with the start and end dates of the trial, as well as the dates of delivery of the investigational medicinal product.

## Data management and clinical trial report (CTR)

Inspectors should review procedures affecting:

(a) A system for tracking data from case report forms to a database;

(b) Validation of the computerized systems used;

(c) Data management;

(d) A statistical analysis in accordance with the established clinical trial protocol;

(e) The contents of the clinical trial report;

(f) Quality control in use;

(g) A system for verifying the clinical trial report, including verification of genuineness of signature.

## Documentation and archiving of clinical trial data

It should be determined the availability of all essential documents specified in the trial master file (TMF) and other required documents for a specific trial and the possibility of obtaining them during the inspection. The risk-based approach applied in the trial affects the contents of the trial master file.

## Audit

Inspectors should verify the following information and data:

(a) Whether the clinical trial was or was not audited, availability of audit reports;

(b) Qualifications of auditors.

Annex No. 7

to the Rules for Conducting Inspections for
Compliance with Requirements of the
Good Clinical Practice Rules

**Inspection of clinical trials in terms of: bioanalytical part of the trial, pharmacokinetic and statistical analyses of bioequivalence studies**

Bioequivalence studies consist of several parts:

(a) The clinical part, which involves administration of the trial and reference products to the trial subjects and collection of biological samples (usually plasma or serum, sometimes whole blood, urine or any other suitable matrix) from trial subjects is not covered by this annex and subject to assessment in accordance with Annex No. 4 to these Rules;

(b) The bioanalytical part, in which the concentrations of the active substance and/or product(s) of its biotransformation in such biological samples are measured;

(c) A pharmacokinetic analysis, in which PK parameters are calculated based on the concentrations of the active substance;

(d) A statistical comparison of PK parameters obtained for the investigational and reference products.

This annex brings together specific elements that can be checked during inspection of the bioanalytical part, and PK and statistical analyses of bioequivalence studies. The elements to be inspected are selected depending on the inspection scope and is to be detailed in the inspection plan.

During the inspection, documents and data are reviewed related to:

(a) storage of biosamples;

(b) bioanalytical method validation;

(c) bioassays;

(d) pharmacokinetic and statistical analyses of the trial data (if these were performed).

When applying a risk-based approach to the planning and conduct of clinical trials, inspectors should take this approach into account during the inspection if it is implemented in the inspected clinical trial. Risk adaptations shall be clearly described and justified in terms of risk assessment and mitigation.

## I. Bioanalytical Part of Bioequivalence Studies

### 1. General arrangement of the bioanalytical site

#### Activities

The main issues to be addressed are as follows:

(a) The nature of the laboratory's activities;

(b) The portion of bioequivalence studies in the structure of activities;

(c) Personnel proficiency in the analytical methods used, especially with regard to complex analytical methods.

#### Personnel

The main issues to be addressed are as follows:

(a) The organizational design in place at the time of inspection and during the conduct of the inspected trial;

(b) The number and categories of personnel employed;

(c) Qualifications, training and experience of the personnel;

(d) The individual workload of the personnel involved.

### Quality assurance system

The main issues to be addressed are as follows:

(a) The quality assurance system in place at the laboratory;

(b) The existence, availability, accessibility and validity of standard operating procedures (SOPs);

(c) A list of standard operating procedures used in the trial;

(d) Working knowledge of standard operating procedures by responsible persons.

### Facilities and equipment

During the inspection the appropriateness of the infrastructure and equipment, their fitness for the laboratory's activities and the bioequivalence study being inspected should be verified.

### Document archiving

The main issues to be addressed are as follows:

(a) The nature of the documents stored;

(b) Place of archiving;

(c) Control of access to the archiving place;

(d) Conditions of storage and protection of documents;

(e) The person in charge of archives;

(f) Recording the document flow;

(g) Duration of document retention;

(h) Conditions of temporary document seizure (if applicable).

## 2. Sample tracking

### Acceptance

It is acceptable to inspect the overall sample handling processes (procedures) at the inspected entity, including:

(a) Responsibility for accepting and handling biological samples;

(b) The acceptance system, including out-of-hours (days or hours);

(c) Registration of samples;

(d) Control tests performed during acceptance.

The issues addressed in detail in the inspected trial are as follows:

(a) Date and time of sample acceptance, as well as confirmation of the acceptance;

(b) A list of samples received for each shipment;

(c) Conditions of sample transportation (temperature and other relevant physical (chemical) environmental factors);

(d) The state of the samples at the time of acceptance;

(e) Any abnormalities noted;

(f) Known stability of the samples (according to the validation report).

## Storage

For samples collected for a trial under inspection, the following should be checked:

(a) Storage conditions for trial samples;

(b) Conformance of storage conditions to the protocol and storage conditions used during method validation;

(c) Assessment of the sample confusion risk;

(d) Identification of the freezer used;

(e) Freezer temperature logs;

(f) Calibration of the thermometer and its traceability to national or international standards;

(g) Alarms and other control measures;

(h) Labeling of samples (if still available);

(i)Documentation of the freeze–thaw cycles to which the samples have been subjected.

Destruction

The date of destruction or return of samples should be verified.

3. Sample analysis

The bioanalytical method used to analyze the samples should be verified:

(a) **Method** description. The consistency of the trial report with the standard operating procedures covering the bioanalytical method and other applicable documents should be checked;

(b) Equipment. The main aspects to be addressed for the equipment used in the trial (including scales and pipettes) are:

Equipment identification data (manufacturer, model);

The availability of the equipment. If a piece of equipment is no longer at the site at the time of the inspection, verification of documentation to show that the required equipment was indeed available at the time of the trial should take place;

Availability of operating instructions;

Observance of special conditions required for the inspected trial (if any);

Documentation relating to equipment qualification, inspections and maintenance;

(c) Reagents. The main issues to be addressed are as follows:

labeling of reagents, including expiration date;

traceability of the origin of the reagents used;

observance of certain storage conditions (if any);

(d) Reference standards. The main issues to be addressed are as follows:

availability and content of certificates of analysis;

validity dates;

storage conditions;

conditions of access to reference samples;

(e) Calibration, control samples. The main issues to be addressed are as follows:

dates and conditions of preparation of stock and working solutions, as well as calibration and control samples, and the number of aliquots to be formed for each sample;

accurate calculations of nominal concentrations;

conditions and duration of storage of stock solutions, working solutions, calibration and control samples compared to their stability should be in accordance with the information specified in the validation report;

the matrix used, including anticoagulant if available;

storage conditions of the blank matrix before use (temperature, duration, freezing and thawing cycles).

The main issues to be addressed for calibration of each analytical run are as follows:

number of calibration samples;

response function used, including weighing (if any);

acceptance criteria for the calibration curve;

exclusion criteria for the calibration curve;

Method development

A summary of the source and development of a bioanalytical method can help identify the critical stages of the procedure.

## Method validation

The main issues to be addressed are as follows:

(a) Validation protocol;

(b) Validation dates;

(c) Adequate level of documentation of all operations;

(d) Completeness of the validation report when compared to the different experiments performed;

(e) Consistency of the validation report with source documents;

(f) Chromatogram integration;

(g) Misses in the sequence of aliquot injection;

(h) Variation in the response of the internal standard;

(i)Settings and content of the audit trail;

(j)Exclusion of calibration samples (if any).

The main validation parameters are as follows:

(a) Stability of:

stock solutions,

samples (shelf, freeze–thaw cycles, long-term);

extracted samples before they are injected (if applicable);

(b) Specificity and selectivity;

(c) Accuracy;

(d) Precision;

(e) Quantitation limit;

(f) Response factor;

(g) Carryover

(h) In case of mass-spectrometry-based methods, the matrix effect;

(i)Dilution effect (if applicable);

(j)Where applicable, the effect of an anticoagulant used to prepare calibration and/or QC samples is different from the anticoagulant used to collect samples during the trial.

Biosamples

The main issues to be addressed are as follows:

(a) The nature and completeness of available documentation;

(b) Adequate level of documentation of all operations;

(c) Completeness of the analytical report;

(d) Number, date and content of analytical runs;

(e) Identification data of samples and test tubes;

(f) Assessment of the sample confusion risk;

(g) Assessment of the sample cross-contamination risk;

(h) Chromatogram integration;

(i)Calculation of concentrations;

(j)Meeting predetermined exclusion criteria for calibration samples;

(k) Acceptance criteria for analytical runs and compliance with predetermined criteria;

(l)Audit trail settings and the information captured by the audit trail;

(m) Misses in the injection sequence;

(n) Variation in the response of the internal standard;

(o) Practical aspects of repeated analysis and criteria for selecting a result to report;

(p) Maintenance of blinding, if provided for in the clinical trial protocol;

(q) Practical aspects of data transfer;

(r) Consistency of the analytical report with source documents;

(s) Maintaining blinding until the bioanalytical phase is complete (if applicable).

## II. Pharmacokinetic and statistical analyses

### 1. Pharmacokinetics

The main issues to be addressed are as follows:

(a) Current quality system;

(b) Identification, qualifications and responsibilities of the personnel involved,

(c) Software in use,

(d) Practical aspects and data input check,

(e) Time points of sampling,

(f) A method used to calculate PK parameters,

(g) Dataset to calculate terminal half-life (if applicable),

(h) Consistency of the source data with the clinical trial report.

It is reasonable to recalculate PK parameters prior to inspection.

### 2. Statistical analysis

The main issues to be addressed are as follows:

(a) Current quality system;

(b) Identification, qualifications and responsibilities of the personnel involved,

(c) Software in use,

(d) Practical aspects and data input check,

(e) Line listings and tables of results,

(f) Consistency of the source data with the PK parameters calculated and the clinical trial report.

If required, statistical analyses are subject to be repeated before or during the inspection.

Annex No. 9

to the Rules for Conducting Inspections for Compliance with Requirements of the Good Clinical Practice Rules

(form)

**REPORT**
**on a Pharmaceutical Inspection for Compliance of the Clinical Trial of a Medicinal Product for Human Use with the Good Clinical Practice Rules**
(Title Page)

_____
(name of the entity under inspection)

_____
(name of the pharmaceutical inspectorate)

_____
(address, phone number, e-mail, website
in the information and telecommunications network "Internet")

Checking the conduct of the clinical trial of a medicinal product for human use for compliance with the Good Clinical Practice Rules approved by Decision No. 79 of the Eurasian Economic Commission's Council dated November 3, 2016.

_____
(name of the entity under inspection)

Address:

_____

Grounds: _____

1. Administrative information

| | |
|---|---|
| Trial medicinal product | |
| Comparator | |

| | |
|---|---|
| Application | |

| | |
|---|---|
| Authorization number: | |
| Name and location of the inspected entity | |

| | |
|---|---|
| Clinical trial | |
| EudraCT number | |
| Sponsor | |
| Trial protocol code | |
| Name of the trial protocol | |
| Total number of trial sites | |
| Total number of subjects | |
| Date and version of the clinical trial report | |

| | |
|---|---|
| Information on the inspected entity | |
| Name of the inspected entity | |
| Principal Investigator (if applicable) | |
| Location | |

| | |
|---|---|
| Master data of the inspected entity: | |
| Number of trial subjects | |
| The first visit of the first subject (date) | |
| The last visit of the last subject (date) | |
| Screened subjects (number) | |
| Randomized subjects (number) | |
| Number of subjects discontinued and/or withdrawn from the trial as of data lock point according to the second clinical trial report | |

| | |
|---|---|
| Inspection dates | |

| Inspectors | Authorized authority | Member State | Dates of visit |
|---|---|---|---|
| Lead Inspector | | | |
| Inspector | | | |
| Expert | | | |
| Trainee (observer) | | | |

2. General information

| | | |
|---|---|---|
| Grounds for inspection | | |
| Personnel involved in the trial and participated in the inspection | Full name . | Function |
| | | |
| External experts who participated in the inspection | Full name . | Function |
| | | |

3. Resources of the inspected entity

| | | | | | |
|---|---|---|---|---|---|
| Name of the inspected entity | | | | | |
| Personnel | | | | | |
| Personnel qualification and training | | | | | |
| Premises | | | | | |
| Equipment | Name of equipment | Intended use of equipment | Serial number | Validation report No. | End of validation period |
| | | | | | |
| Computer systems | Name of the system | Version | Purpose | Certificate of validation and integrated validation report | Date of integrated validation report |
| | | | | | |
| | | | | | |

4. Administrative aspects of the trial

| | |
|---|---|
| Authorized authority of the State where the inspection is conducted | |
| Independent Ethics Committee | |
| Other committees, other validation or registration required | |
| Agreements | |
| Insurance | |

5. Trial master file

| | |
|---|---|
| Preparation, version control and content of key documents | |
| Completeness, accessibility, content and structure of the trial master file and site investigator file | |

| | | | |
|---|---|---|---|
| 6. Conduct of the clinical trial | | | |
| 7. Management of the trial by the Sponsor and/or contract research organization | | | |
| 8. Safety reporting | | | |
| 9. Investigational drug product (storage, transportation, use, etc.) | | | |
| 10. Management of clinical data | | | |
| 11. Source data review and/or verification | | | |
| 12. Clinical trial monitoring | | | |
| 13. Imaging diagnostics (checkups) | | | |
| 14. Management of clinical samples | Clinical samples (at the clinical trial site) | Clinical samples (at the laboratory or analytical site) | |
| | | | |
| | | | |
| | | | |
| 15. Laboratory | | | |
| 16. Bioanalysis (Pharmacokinetics) Laboratory | Methods used | Method validation and report | Results |
| | | | |
| | | | |
| 17. Pharmacokinetic analysis | | | |
| 18. Statistical analysis | | | |
| 19. Reports:<br>Clinical trial report;<br>Bioanalytical report | | | |
| 20. Quality management system | Standard operating procedures (SOPs) | Quality control | Quality assurance |
| | | | |
| | | | |

21. Identified nonconformities, recommendations and conclusions

| Number of nonconformity | Number and/or name of the Good Clinical Practice section | Description of the nonconformity | Party responsible | Criticality |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |

| Critical nonconformities (CNC) | |
|---|---|
| Definition | Any nonconformities that adversely affect the quality, integrity and adequacy of the clinical trial data or have a negative impact on the rights, safety and well-being of trial subjects. |

| Major nonconformities (MaNC) | |
|---|---|
| Definition | Nonconformities that cannot be categorized as critical, but are capable of adversely affecting the quality and integrity and/or adequacy of the clinical trial data, or are capable of adversely affecting the rights, safety and well-being of the trial subjects |

| Minor (other) nonconformities (MiNC) | |
|---|---|
| Definition | Nonconformities that do not affect the quality and integrity of the data and do not adversely affect the rights, safety and well-being of trial subjects |

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| Recommendations | |
|---|---|
| Preliminary conclusion | |

The pharmaceutical inspection report was drawn up and signed by:

Full names, positions of the inspection team members

(signatures of the inspection team members)

Annex
to the Report on a pharmaceutical inspection
for compliance of the clinical trial of a
medicinal product for human use
with the Good Clinical Practice Rules

**RESPONSES**
**From the Inspected Entity**

Date of receipt of responses by the inspector: DD/MM/YYYY

The following attached documents contain the inspected entity's response:

1.

2.

3.

…..

Annex
to the Report on a pharmaceutical inspection
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**EVALUATION OF THE RESPONSES**
**From the Inspected Entity**

Final conclusions
on nonconformities identified during inspection

Date of evaluation: dd/mm/yyyy

| |
|---|
| Assessing the significance of the findings for the overall trial |
| |
| Data quality and compliance with Good Clinical Practice |
| |
| Recommendation on the acceptability of clinical trial data |
| |
| Recommendations for further measures to improve operation in accordance with Good Clinical Practice |
| |

Full names, positions of the inspection team members
(signatures of the inspection team members)

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