ANNEX
to Recommendation No.
of the Eurasian Economic Commission's
Board
dated , 20

GUIDELINES
on Planning Risk-Based Inspections of Pharmaceutical Manufacturers

I. General Provisions

1. These Guidelines establish approaches to determine the frequency of pharmaceutical inspections of medicine manufacturers for compliance with the requirements of the Good Manufacturing Practice of the Eurasian Economic Union, approved by Decision No. 77 of the Council of the Eurasian Economic Commission dated November 3, 2016 (hereinafter, the inspection, the Good Manufacturing Practice), their frequency, scope, periodicity, and duration. These Guidelines are used by each pharmaceutical inspectorate of the Eurasian Economic Union Member States (hereinafter, the Member State, the Union) as a basis for the development and implementation of the annual inspection timeline, as well as for the identification of priority production sites to be inspected when planning the frequency and scope of inspections. The purpose of this document is to provide a risk management tool for the quality of medicines that may be used by pharmaceutical inspectors.

2. These Guidelines apply to determining the frequency of routine inspections and planning inspections of manufacturers of medicines.

3. These Guidelines may also be applied when conducting a risk-based inspection with the aid of remote communication tools.

4. These Guidelines describe follow-up actions, such as changing a risk rating after receiving new information about a production site or product (e.g., quality defects, product recalls, medicine test results).

5. These Guidelines do not apply to:

the inspection procedure;

planning of inspections (checks, assessments) when licensing pharmaceutical activities (during initial licensing and making amendments to previously issued licenses for production of medicines) in terms of production of medicines or in case of detecting a poor-quality (counterfeit) medicine and other cases;

inspection of production sites that have not been previously inspected;

inspections scheduled as part of marketing authorization procedures.

II. Terms and Definitions

6. For the purposes of these Guidelines, the terms below shall have the following meaning:

“internal risk” is the risk inherent to a production site that reflects the complexity of the site, its processes and the medicines produced, as well as the criticality of the medicines produced or services provided by the production site and/or other activities conducted at the production site;

“good manufacturing practice compliance risk” describes the extent to which a production site complies with the requirements of the Good Manufacturing Practice and is based on the results of the most recent routine inspection, taking into account the quantity and classification of any non-conformities identified.

III. Impact of the risk assessment procedure on the inspection scope and frequency

7. The risk ratings assigned to a production site are based on an assessment of two different types of risk: internal risk and risk of non-compliance with good manufacturing practice requirements.

These risks are defined in Annex No. 2 to these Guidelines.

Once the internal risk and the risk of non-compliance with good manufacturing practice requirements have been identified, the two risks are combined using a simple matrix to establish the risk level of the production site. This risk assessment is taken into account when determining the frequency of routine inspections and planning inspections of the production site. This method is used to assess the risk level on the basis of which an inspection is prepared and performed, including the decision to perform an inspection with the aid of remote communication tools.

8. Inspections are performed at intervals specified in the Rules for Conducting Pharmaceutical Inspections for Compliance with Requirements of the Good Manufacturing Practice of the Eurasian Economic Union, approved by Decision No. 83 of the Council of the Eurasian Economic Commission dated November 3, 2016 (hereinafter, the Rules for Inspections), since the lack of such intervals may lead to reduced compliance with the requirements of the Good Manufacturing Practice of the Eurasian Economic Union or the emergence of significant non-conformities.

9. The following factors may additionally be considered in determining the scope and schedule of the next production site inspection:

knowledge about the plant (compliance with regulatory requirements, information about the plant and production site);

results of quality assessment of manufactured medicines in testing laboratories of the Member States and third countries;

quantity and significance of quality defects, as well as cases of product recalls;

amendments to the marketing authorization application affecting the production site;

delayed amendments to the marketing authorization application made by the medicine manufacturer;

information on poor quality of the medicines received from authorized authorities of third countries (if any);

information received from authorized authorities of the Member States and third countries on the results of previous inspections and identified non-conformities with the requirements of good manufacturing practice;

changes in buildings, equipment, processes, personnel affecting the medicine.

10. The major conditions for consideration of information submitted by third countries on the compliance of the production site with the requirements of good manufacturing practice are:

the fact that the production site has been inspected by a pharmaceutical inspectorate of a Member State or by authorized authorities of third countries;

the fact that the pharmaceutical inspectorate of a Member State has received sufficient information on compliance of the production site with good manufacturing practice.

Information from authorized authorities of third countries may be considered as “trusted” if there are bilateral agreements between states and if the requirements of good manufacturing practice of third countries are similar to the requirements of the Union’s Good Manufacturing Practice.

The scope of the next inspection shall be defined by the results of the risk assessment, as well as the following factors:

the required area and depth of the next inspection;

the required duration of the next routine inspection;

the necessary number of inspectors to be assigned to the next inspection;

the necessity to have experts with specialized knowledge or experience on the inspection team at the next inspection.

11. In determining the required area and depth of the next inspection, the inspector shall consider the following factors:

areas where significant and critical non-conformities were identified during the last inspection;

areas that were not inspected (or that were not inspected in detail) during the last inspection;

areas that were considered under-resourced at the last inspection;

any other area that in the opinion of the inspector requires detailed examination at the next routine inspection.

IV. Determining the duration and frequency of inspections

12. The duration (in days) of each production site inspection shall be determined in accordance with Annex No. 1 to these Guidelines and taking into account the quality system requirements of the pharmaceutical inspectorate of a Member State.

13. The inspection duration may be adjusted as necessary in accordance with the inspection plan (schedule).

14. Production sites are classified according to the medicines and dosage form manufactured, as well as the process operations.

15. The planned inspection duration may be adjusted depending on the following factors:

inspection type (covers all manufactured medicines and dosage forms, as well as the process operations or only a part of them);

production site complexity (size, variety of products);

production process complexity (type and sequence of operations, control processes applied);

complexity of medicines and their therapeutic potency;

the effect a medicine has on patients, as well as the production of medicines listed as essential medicines;

data on production compliance with the requirements of good manufacturing practice based on the results of previously conducted inspections.

16. The next planned inspection date shall be determined by adding the date when the last inspection is completed and the result obtained with the use of the risk assessment method according to Annex No. 2 to these Guidelines.

V. Risk analysis

17. When using this risk assessment tool, a risk assessment protocol for planning inspections (hereinafter, the protocol) shall be completed for each production site in accordance with Annex No. 2 to these Guidelines. The lead inspector and other members of the inspection team shall complete the protocol after the last inspection is completed. The head of the pharmaceutical inspectorate or a designated lead pharmacy inspector shall review and sign the completed protocol. The completed protocol shall be kept in the applicant’s (manufacturer’s) master file.

18. Part A of the protocol contains general information (name of the plant (production site), its address, number and date of the license for production of medicines, and certificate of production compliance with the requirements of good manufacturing practice.

19. Part B of the protocol assesses the risk inherent to this production site.

There are two risk factors to consider:

a) complexity of the production site, production processes, and products;

b) criticality of the products made at the production site (or criticality of services provided by the production site (e.g., quality assurance under a contract).

20. Complexity and criticality of a production site shall be assessed in accordance with Annex No. 1 to these Guidelines.

21. Each risk factor is assigned a score of 1, 2, or 3 (where 1 is the lowest level of complexity and/or criticality and 3 is the highest level).

22. The matrix in Table 1 is presented to combine the scores of two factors (complexity and criticality) to assess internal risk for the production site.

A score of 1 or 2 represents low internal risk, 3 or 4 is medium internal risk, and 6 or 9 means high internal risk.

Table 1

Internal Risk Assessment Matrix

Complexity	Criticality		
	1	2	3
1	1 (low)	2 (low)	3 (medium)
2	2 (low)	4 (medium)	6 (high)
3	3 (medium)	6 (high)	9 (high)

23. Part C of the protocol assesses the risk based on non-conformities identified during the previous inspection of the production site.

24. If one of the previous inspections was not complete (e.g., did not cover all stages of production and identified a poor-quality medicine in circulation), the non-conformities identified at that inspection shall be taken into account as well as those identified at subsequent inspections.

25. Table 2 summarizes the risk assessment associated with assessing compliance with good manufacturing practice at a specific production site.

Table 2

Determining the Risk Associated with Assessing Good Manufacturing Practice Compliance

Description of non-conformities	Degree of risk associated with assessing conformity with regulatory requirements
1 or more critical non-conformities or over 5 significant ones	high
up to and including 5 significant non-conformities	medium
no critical or significant non-conformities	low

26. Depending on the quantity and classification of non-conformances, the risk of non-compliance with good manufacturing practice is assessed as high, medium, or low.

27. Production sites with a high degree of risk associated with assessing good manufacturing practice compliance are included in the inspection plan in accordance with the provisions of these Guidelines based on the results of the corrective and preventive action plan.

28. The risk assessment tool is used to calculate the inspection frequency. The risk assessment associated with assessing good manufacturing practice compliance shall take into account non-compliances identified during both the initial inspection and the re-inspection.

29. Taking into account the results of assessing the risk associated with good manufacturing practice compliance, the following inspection approaches are applied:

production sites having a high level of risk associated with assessing good manufacturing practice compliance shall be inspected over a longer number of days and/or by an increased inspection team;

production sites with a high risk of non-compliance with good manufacturing practice shall be re-inspected following the performance of the corrective and preventive action plan.

30. In Part D of the protocol, internal risk and risk of non-compliance with good manufacturing practice are combined and used to determine the risk rating of a production site. There are three possible risks: A, B, or C (where A is a low-risk production site, C is a high-risk production site).

Table 3

Matrix of Risk Rating Assigned to a Production Site

Risk of Non-Compliance with Requirements of Good Manufacturing Practice	Internal risk		
	low	medium	high
Low	risk rating = A	risk rating = A	risk rating = B
Medium	risk rating = A	risk rating = B	risk rating = C
High	risk rating = B	risk rating = C	risk rating = C

31. Part E of the protocol determines the recommended frequency of production site inspections on the basis of the risk rating identified in Part D of the protocol.

Production sites shall be inspected:

if the risk rating is A, every 2–3 years;

if the risk rating is B, every 1–2 years;

if the risk rating is C, at least once a year.

The actual frequency of inspections within a risk rating (A, B, or C) depends on the quantity and classification of non-conformities identified during the last inspection. The frequency of inspections is further adjusted to take into account the internal and good manufacturing practice risk scores that make up the overall risk rating.

32. If the Inspectors who performed the last inspection disagree with the recommended inspection frequency established in determining the overall risk rating, they shall justify and document the cause for disagreement. Aspects to be considered:

reliability of the quality management system at the production site;

the overall history of non-compliance with good manufacturing practice requirements, taking into account recurring non-conformities and incomplete elimination of non-conformities identified during inspections;

insufficiency and inefficiency of measures taken to eliminate non-compliance.

The Lead Inspector shall propose a new inspection frequency, which is agreed with the head of the pharmaceutical inspectorate.

It is allowed to inspect medicine manufacturers using remote communication tools in cases not specified in Annex No. 2 to the Rules for Inspections, if the overall risk rating of the production site (including internal risk and risk of non-compliance with good manufacturing practice requirements) is determined as low.

Part F of the protocol shall be completed immediately after the inspection has been performed or after the inspection report has been signed. There are four sections to be completed in this part:

recommended areas and depth of the next routine inspection,

duration of the next inspection,

the number of inspectors necessary for the next inspection,

the need to include experts with specialized knowledge or experience in the inspection team for the next inspection.

Data from Parts E and F of the protocol shall be used to prepare the inspection plan (schedule).

33. Part G of the protocol shall include the name, initials, date, and signature of the inspectors who performed the risk analysis and the head of the pharmaceutical inspectorate of a Member State or a designated pharmaceutical inspector.

VI. Revising and updating the risk analysis

34. Risk analysis results and ratings shall be reviewed when a Member State pharmaceutical inspectorate receives new information that may change the risk rating of a production site and lead to a change in the scope or frequency of the next inspection, for example:

about product quality defects;

about product recalls;

about the results of trials when medicines are withdrawn from the market;

about investigations conducted by the competent authorities;

about changes at the production site, etc.

35. If changes made to a marketing authorization application for a medicine or to a medicine manufacturing license mean that a production site's activities are expanding or significantly changing, which may considerably affect the complexity or criticality of the processes associated with the site, such changes shall be treated as new information.

36. Significant changes in staffing levels may indicate a change in the complexity of the production site, which could impact internal risk or possibly indicate a reduced availability of quality assurance resources, which could subsequently lead to issues with good manufacturing practice compliance.

37. The manufacturer's response following the last inspection report is also considered as new information. In reviewing it, the pharmaceutical inspectorate may decide that certain aspects of the said response shall be

thoroughly examined during the next inspection. This decision affects the scope of the next inspection.

38. The new information specified in paragraphs 34–37 may lead not only to a change in the recommended scope of the next routine inspection, but also to a change in the recommended frequency of the next routine inspections.

ANNEX No. 1

to the Guidelines
on Planning Risk-Based Inspections
of Pharmaceutical Manufacturers

Assessment of
complexity and criticality of the production site

No.	Internal risk factors. Calculation procedure
1	Complexity Refers to the complexity of the production site, the production processes and the products. (Note. The site master file (if any) and the latest inspection report may be useful sources of information to assign a complexity score). Possible scores: 1, 2 or 3. Production sites with a low score on internal risk factors have a low complexity of the site design, manufactured products and process operations (production processes). The following shall be taken into account when calculating an internal risk factor: (a) general indicators of the production site complexity: production site size (large sites are assessed as more complex compared to small sites); the quantity of different production processes that are used at the site; purpose of production equipment and facilities (e.g., air treatment systems). The sites designed for the production of various medicines (not dedicated individually to the production of specific medicines) are considered more complex than others; number of workers on the site, as more workers lead to higher complexity; number of countries to which the site's products are shipped. A larger number usually leads to higher complexity; number of buyers (distributors) of products. A large number leads to higher complexity; if a production site is a contract manufacturer or contract laboratory, it may be considered relatively complex. b) general complexity indicators: sterile and aseptic production processes are considered very complex; parametric release is considered a very complex process;

	number of critical control points in the production process. Typically, processes with their greater number may be considered more complex; types of manufactured products. Some medicines, such as low concentration / potent dosage forms or slow release dosage forms, may be more complex to manufacture than others (e.g., immediate release pills), therefore the complexity of their production process is assessed as higher; number of process operations in a non-sterile production process. A larger number leads to higher complexity; repackaging operations. Repackaging of an already packaged batch may be considered a moderately complex process; recycling or waste recovery may increase the site complexity; production of biologics; the extent to which third-party services are utilized at the production site. As a rule, significant use of contract manufacturers or contract laboratories leads to higher complexity. c) general indicators of the complexity of products: quantity of components that make up the finished medicine. A larger quantity usually leads to higher product complexity. For example, a package of an injection medicine may contain 4 components (freeze-dried powder in a vial, a vial with a diluent, a transfer needle and instructions for medical use, whereas a package of pills may contain only a blister pack and instructions for medical use (an insert)); products requiring special storage and transportation conditions (e.g., cold chain conditions or having a short shelf life such as radiopharmaceuticals); When considering product complexity, a situation shall be modeled in which a pharmaceutical inspector with access to a medicine comes up with a response to the question, “What aspects of this medicine in this package make it complex?” Scoring: Assign 1 point to sites with a low overall level of complexity, Assign 2 points to sites with a moderate overall level of complexity, Assign 3 points to sites with a high overall level of complexity. Note. When rating overall complexity, select the score (1, 2 or 3) that best reflects the various individual complexity ratings that have been assigned to the production site, its process and products. In cases of insufficient information or knowledge about the complexity of the processes and products associated with the production site, the middle score of 2 shall be assigned.
2	Criticality Criticality relates to the importance of the availability of products made at a given production site or the importance of the services provided by the production site. An example of a critical service provided by the site would be analytical testing performed for several other companies.

	Useful sources of information to assign a criticality score are the production site master file (if any) and the latest inspection report. Possible criticality scores are 1, 2 or 3. Scoring: Assign a high score (3) to production sites that are known to make core products or that provide an essential service that may not be provided by anyone else. These may be production sites that are the only ones in the country that produce the essential products (e.g., essential vaccines, critical blood products, etc.). Note: It should be borne in mind that being a major or sole supplier of an essential product does not pose any risk to the product quality, but lack of that product poses a risk to product availability. Test methods (and associated equipment) used at these sites may not be replicated at other sites (e.g., cold chain or storing products having a short shelf life as such radiopharmaceuticals) These may be production sites that perform contract production operations or testing for other manufacturers, and a breach of terms and conditions would have a significant impact on product availability. The low score (1) is assigned to production sites that make products, the lack of which would not affect medicine provision to the public and the health care system. These production sites are not the sole supplier of any critical products (e.g., an essential vaccine, critical blood product, etc.). Test methods (and associated equipment) used at the site may be freely replicated or used by other laboratories. These sites do not provide contract manufacturing or product testing services for many other manufacturers where disruption of these services would have a significant impact on product availability. Assign the middle score (2) to production sites that fall between the above mentioned site types. In cases of insufficient information or knowledge about the criticality of the processes and products associated with the production site, the middle score of 2 shall be assigned.

ANNEX No. 2

to the Guidelines
on Planning Risk-Based Inspections
of Pharmaceutical Manufacturers

PROTOCOL
on Risk Assessment for Inspection Planning

Part A. Basic information about the production site	
Name of the production site(s)	
Address of the production site(s)	
Whether a finished medicine or an active pharmaceutical substance is produced	
Availability of a certificate of production compliance with the requirements of good manufacturing practice, date of issue	
Information on production operations	
Date of the last routine inspection	
Inspection date	
Lead Inspector	

Part B. Internal Risk of the Production Site			
Risk factors	Group 1	Group 2	Group 3
Complexity of the production site, production processes and products is assessed as:			
The criticality of the products or the criticality of the test methods or services provided is assessed as:			

Internal Risk Assessment Matrix				
	Criticality			Use the matrix above and mark the internal risk of the production site*:*
Complexity	1	2	3	
1	1 Low	2 Low	3 Medium	
2	2 Low	4 Medium	6 High	
3	3 Medium	6 High	9 High	

Low □
Medium □
High □

Part C. Risk with assessing good manufacturing practice compliance (following the inspection)		
The risk is determined using the non-conformity profile established during the inspection:	Low □ Medium □ High □	no significant or critical non-conformities 1 to 5 significant non-conformities: Quantity = 1 or more critical non-conformities or over 5 significant non-conformities (used if required)

Part D. Production site risk rating

Complete the matrix by combining the internal risk score and the risk of good manufacturing practice non-compliance to determine the risk rating of the production site

	Internal risk		
Risk of Non-Compliance with Requirements of Good Manufacturing Practice	low	medium	high
Low			
Medium			
High			

Risk rating assigned to the production site: **A** □ **B** □ **C** □

Part E. Recommended frequency of site inspections

A	Reduced frequency, once every 2–3 years	Using the risk level (rating): 1) Estimated date of the next inspection: _____ 2) The next inspection may be rescheduled for a period not greater than: _____ (month/year)
B	Average frequency, once every 1–2 years	
C	Increased frequency, at least once a year	

Part F. The recommended scope of the next routine inspection

If new information about the production site is received prior to the next inspection and it requires a change in the risk rating and scope of inspection, Part F shall be updated. This information may be: about quality defects, recalls, test results, quality-related investigations, or related to changes in the marketing authorization application for a medicine or medicine manufacturing license.

The recommended area and depth of the next inspection: Consideration shall be given to: areas where non-conformities were identified during the previous inspection, especially significant and critical ones;	

areas that have not been inspected (or were not thoroughly covered by the previous inspection); areas requiring more resources for inspection; planned changes at the production site that may affect the complexity or criticality of the production site's risk level (rating); any other area that the inspector deems necessary to inspect at the next inspection.	
Duration of the next inspection (number of days):	
The number of inspectors necessary for the next inspection:	
Any special knowledge or experience that the pharmaceutical inspectors of the inspection team will need for the next inspection. The need to add experts with specialized knowledge or experience to the inspection team at the next inspection:	
Part G. Signatures and Dates	
Full name of the Lead Inspector: _____ signature _____ date_____ Full name of the Inspector: _____ signature _____ date_____ The head of the pharmaceutical inspectorate or the designated pharmaceutical inspector: Full name: _____ signature _____ date_____	

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