ANNEX

to Recommendation of the Board
of the Eurasian Economic Commission
No. _____ dated _____, 20

GUIDELINES
for temperature mapping of medicine storage areas

I. General provisions

1. These Guidelines were developed for organisations that are manufacturing medicines, organisations engaged in wholesale trade of medicines, medical organisations, pharmaceutical inspectorates and authorised bodies (expert organisations) of the member states of the Eurasian Economic Union (hereinafter referred to as the Member States and the Union) in regard to activities related to the registration and control of temperature distribution in medicine storage areas; it was developed considering the Rules of Good Distribution Practice within the Eurasian Economic Union approved by Decision No. 80 dated November 3, 2016 of the Council of the Eurasian Economic Union.

2. The Guidelines provide recommendations on temperature mapping, systematic mapping of cold rooms, freezers and other temperature-controlled areas and do not address issues related to the operation of small equipment (e.g. household refrigerators and freezers), its qualification ensuring suitability for storing temperature-sensitive products, or the operation of mobile cold chain equipment that is regulated by the legislation of the Member States.

II. Definitions

4. For the purposes of these Guidelines, the terms below shall have the following meanings:

"hot spot" means maximum temperature values registered during mapping, however, within the allowable temperature range;

"sensor" means a mechanical device, or a digital or analogue transducer, that produces a mechanical or electrical signal transmitted to a device or controller for subsequent interpretation;

"area" means a room, or part of a room, designed for the storage of medicines;

"mapping" is a documented study of the temperature distribution profile within a storage area, including identification of locations with minimum and maximum values (cold and hot spots);

"qualification" means documented actions that demonstrate that equipment or auxiliary systems are properly installed, function properly, and do produce the expected results;

"operational qualification" means documented actions that certify and confirm that facilities, equipment, and utilities are functioning in accordance with design specifications;

"operational qualification" means documented actions that confirm that facilities, equipment, and utilities are functioning in accordance with design specifications;

"performance qualification" means documented actions that demonstrate that facilities, equipment, and utilities functioning jointly can be effectively and consistently operated as provided by the approved process and in accordance with approved specifications;

"medicinal products that are sensitive to temperature changes and/or storage and transportation times (SMPs)" are medicinal products that lose their properties, up to complete inconsistency with their intended use, when stored and transported in conditions not corresponding to the established environmental parameters and/or time period;

"data logger" is a measuring instrument that provides registration of data for a specified period of time and storage of the obtained data, while maintaining their integrity and allowing transmitting the obtained electronic readings to another device (e.g., PC);

"temperature controlled environment" means any environment with temperature that is maintained by active or passive means within predetermined precise limits that differ from ambient conditions;

"temperature fluctuations" are changes (variations) in storage temperature;

"temperature deviations" mean the measured temperature values beyond the established storage range of temperature-sensitive products that cause risks to their quality;

"storage temperature" means a temperature range for storage of temperature-sensitive products, specified in regulatory documents;

"refrigerating equipment" means any equipment designed to automatically maintain temperature in enclosed spaces or thermally insulated chambers;

"cold spot" means minimum temperature values registered during mapping, however, within the allowable temperature range.

III. Temperature mapping

5. Mapping is a procedure performed to analyse the temperature distribution in a storage area with specific temperature requirements, as well

as to identify hot and cold spots; it is an integral part of the qualification of storage areas. Additionally, temperature mapping can also be carried out for other storage areas (e.g. receiving area, forwarding area).

6. Mapping may be aimed at determining the air temperature profile in an empty and/or loaded storage area during operation to identify areas that are not suitable for the storage of temperature-sensitive products.

7. The data obtained during mapping are the source of information required to ensure that medicinal products that are sensitive to temperature changes and/or storage and transportation times are stored and transported according to recommended temperature requirements.

8. Temperature mapping is conducted for each temperature-controlled storage area prior to operation. Periodic re-mapping is recommended to confirm that the storage area and the equipment used therein meet the established performance specifications in accordance with the requirements. Re-mapping should be performed in the following cases: changes in the dimensions and configuration of the storage area or racking equipment (more than 30%) that affect the loading of the room or air circulation; or replacement of refrigerating equipment in case of changes in the temperature requirements of storage in a particular zone (e.g., actual: + 2 °C to + 8 °C, changed to: + 8 °C to + 15 °C).

It is also recommended to perform a re-mapping if unexplained deviations outside the established operating ranges are detected during the analysis of temperature monitoring results.

It is allowed to change the settings of the refrigerating equipment within the specified range of storage temperature for temperature-sensitive products without re-mapping.

Along with temperature mapping in temperature-controlled rooms used for storage of medicinal products that are sensitive to temperature changes

and/or storage and transportation times, which are subject to a negative impact of high relative humidity and which are not protected from such impact by their own packaging, the relative humidity level for such products should be controlled.

9. Mapping involves the following steps:

a) preparation of the mapping protocol;

b) mapping;

c) development of the mapping report;

d) implementation of corrective actions, other actions and recommendations specified in the mapping report and, if required, re-mapping to confirm the efficiency of the actions performed.

IV. Equipment

10. Data loggers that meet the following requirements should be used during mapping to ensure efficient analysis of temperature distribution in the storage area:

a) to be technically suitable for the task set and for operation in the analysed environmental conditions;

b) to ensure reliable registration of data indicating temperature changes over time;

c) to have an appropriate range of measured temperatures to register the minimum and maximum values of the expected temperature;

d) to provide the user with the possibility to set the data registration period at 1 to 15 min intervals or more, and to have sufficient memory for the data storage, subject to expected study duration, and for the selected registration interval;

e) to have a valid verification date at the moment of temperature mapping. Verification should be carried out in accordance with the legislation

of the Member States. The absolute error of the data loggers should be no more than ± 0.5 °C;

f) to ensure that all accumulated temperature and time results can be transferred to an information system for subsequent analysis;

V. Mapping

11. The mapping should be preceded by the preparation and approval of a test protocol. A single standardised protocol can be used for the mapping of storage areas, regardless of their specific features, with appropriate adjustments and modifications to cover all values of the temperature range.

12. The following sections should be included in the mapping protocol:

Abbreviations and Definitions;

Description and Rationale;

Scope of Application;

Mapping Goals and Objectives;

Mapping Methodology.

13. The Abbreviations and Definitions section should include and describe abbreviations and provide definitions of technical terms used in the protocol.

The Description and Rationale section provides a description of the site for which the mapping is being conducted and an appropriate rationale for this analysis.

The scope of works and mapping tasks are described in detail in the Scope of Application section.

The main objective is to identify temperature fluctuations and deviations that affect the storage areas during the analysis process in order to implement the required corrective actions.

Temperature mapping can be carried out for empty storage areas (e.g., during operational qualification) or for storage areas where temperature-sensitive products are already stored (e.g., during performance qualification).

At least two mapping analyses are recommended for each storage area to confirm the absence of the negative impact of seasonal temperature fluctuations (except for cold rooms and freezers located in controlled environment rooms that are exposed to the limited effect of ambient conditions).

As a rule, one analysis is conducted during the hottest time of the year, and the second one – during the coldest time of the year. This approach allows to analyse the worst-case scenarios of temperature fluctuations and to assess the ability of the storage area to maintain a given temperature throughout the calendar year.

Comparing the results of seasonal analyses can help identify seasonal patterns (fluctuations) in temperature distribution. Such seasonal features (variations) should be differentiated with other site-specific features of the temperature distribution found during a comparative study.

The Mapping Goals (Objectives) section should describe the specific goals (objectives) of the mapping; these may include the following:

a) identification of temperature fluctuations and deviations within selected storage zones;

b) temperature measurement and registration in each storage area section on different days of the week and at different time of the day;

c) description of documenting peculiarities of registered temperature fluctuations and deviations in rooms with controlled environmental conditions;

d) development of recommendations on the organisation of safe storage of temperature-sensitive products in a particular area and determination of areas that are not suitable for storage of these products. The recommendations

should consider all registered temperature fluctuations and deviations found during the analysis, as well as the temperature range allowed for the product.

e) identification of locations for temperature monitoring sensors. If the monitoring system is already mounted, mapping can be used to determine points for sensor relocation (if required).

The Mapping Methodology section should include the following:

a) Selection of the data logger type

The memory size of the measurement device should be sufficient for the data storage considering the expected duration of the analysis and the intervals between data acquisitions. Each data logger should have a valid verification date at the moment of temperature mapping. Verification information (certificate number) should be specified in the mapping report.

Verification should be carried out at the particular verification intervals in accordance with the description of the data logger type.

As a rule, data loggers of the same type are used for temperature mapping to ensure consistency of the analysis results. Corporate employees responsible for programming the data logger and data read-out should have access to the operation manual to correctly make the settings required.

It is recommended to use data loggers equipped with indicators that can be used to determine the device operating status;

b) Selection of persons who perform and who are responsible for mapping

A list of employees responsible for mapping should be defined and developed. All responsible persons should successfully complete a training required to perform their assigned tasks;

c) Analysis of the study object

The following information is recommended to be obtained for each of the storage areas that are subject to temperature mapping:

size of the storage area (length × width × height, or floor area of the room);

a plan (drawing) of the storage areas with various elements, such as shelves or racks, which may affect the uniformity of heating and/or cooling of the study object, or the temperature stability;

location of heating and/or cooling elements, including air ducts and/or ceiling fans, and inlet and exhaust ventilation ducts;

location of previously mounted sensors and temperature control devices (if any);

d) Determination of acceptance criteria

The protocol should include a description of the acceptance criteria established with regard to the specific features of the temperature-sensitive products to be placed in the analysed area. These criteria should include the allowable temperature range within the storage area. In several cases, mapping may be conducted without prior determination of acceptance criteria. This may be performed when determining the types of temperature-sensitive products that can be safely stored in a particular storage area, or selecting actions to improve the temperature characteristics of the storage area and optimizing its use.

If the procedure for temperature mapping (operational qualification) involves opening the door(s), this should be indicated in its methodology and acceptance criteria. The door opening parameters (frequency and duration) should be established;

e) Determination of data logger location points

Data logger location points are determined based on the data obtained during a survey of the storage area. A risk-based approach can also be used to identify such locations.

Data loggers should be arranged as a grid and in such a way that they cover the entire length and width of the storage area. Data loggers should be spaced regularly, where possible. Recommended horizontal grid spacing of temperature measuring devices:

length or width of the storage area up to 10 meters: at least 2 data loggers;

length or width of the storage area up to 40 meters: at least 3 data loggers;

length or width of storage area up to 60 meters: at least 4 data loggers;

length or width of storage area more than 60 meters: at least 5 data loggers.

When planning the sensor placement grid, it is recommended to consider the following:

layout of the storage area indicating the location of equipment to make a controlled environment;

operating parameters and configuration of the storage area (e.g. number of racks, their size, distance between racks, etc.);

product locations (data loggers should be placed in actual and intended product storage locations);

other factors that lead to the increase or decrease in the number of data loggers.

At each grid point, vertical location of data loggers should be additionally organised (layer-by-layer) considering the following requirements:

data loggers should be placed on top of each other at different heights depending on the height of the storage area (not the ceiling height).

the lower point of data logger location is determined by the height of the lower storage level of temperature-sensitive products (pallet or lower level of racking), the upper point – by the height of the upper storage level of temperature-sensitive products (upper level of racking).

Recommended vertical grid spacing of temperature measuring devices:

height up to 1.5 meters from the floor: at least 1 data logger;

height up to 5 meters: at least 2 data loggers;

height over 5 meters: at least 3 data loggers;

Based on the results of data logger placement in the analysed area, each particular point should be assigned a unique number;

f) Registration of data logger locations

It is recommended to enter the data on the locations of data loggers, as well as control values for sensors, in the table according to Table 1, or to place these on the scheme. Properly documented locations of the data loggers used during mapping ensure coordination across all seasonal temperature variation analyses;

g) Labelling and programming of data loggers

Each data logger used during temperature mapping should be assigned its own identification number in accordance with the data logger layout table and should be labelled accordingly, or the serial number of the data logger should be used for identification.

It is reasonable to enter the information on serial numbers of data loggers assigned by the manufacturer in the abovementioned table, as well as additionally assigned identification numbers indicated in additional labelling (if any). Each data logger should be programmed with the same data recording interval, as a rule, 1 to 15 minutes. To synchronise data downloaded from different devices, the same start time should be set for all data loggers. When

setting the start time for the analysis, one should consider the time required to place all data loggers in the specified locations.

Before starting operation, it is recommended to ensure that all data loggers are in good working order and are registering data;

h) Placement of data loggers

The data loggers should be placed at the locations in accordance with the layout and information provided in the data logger placement table. The devices should be mounted and fixed in such a way as to prevent their damage or displacement during routine operations in the storage area; when placed, one should prevent direct contact of sensors with metal, or concrete, or surfaces with similar heat dissipation;

i) Description of the mapping process

Mapping of warehouses and other rooms with maintained environmental conditions should be carried out for at least 7 consecutive days; the analysis duration may be extended, if required. For temperature-controlled equipment that is not affected by critical diurnal or seasonal temperature fluctuations (e.g., cold rooms and freezers), the analysis period may be 24 to 72 hours or longer (if required). If a duplicate refrigeration unit is placed in the storage area, it is reasonable to monitor the operation of both units during mapping, preferably with the same time intervals.

Upon completion of the analysis, information on the serial numbers of the data loggers, their locations in the storage area, and the records made during their placement are re-verified;

j) Data loading and aggregation

The data from each data logger is transferred to a PC for further processing and analysis.

13. The mapping protocol should be approved by the chief executive officer of the organisation and/or an employee authorised to approve the protocol.

If any amendments and/or additions are required to the protocol or if it is required to re-issue the protocol, any change should be clearly stated and the cause for the change should be specified in the protocol.

14. Mapping process

The mapping should be conducted in accordance with the approved protocol. Personnel involved in operations in the storage area should be informed of the mapping to avoid accidental operation failures and disabling of data loggers, or loss of data loggers and data obtained.

At the end of the measuring process, the data loggers should be collected, and the data from their memory should be uploaded to a PC for further analysis, and then they can be turned off.

15. Data analysis

a) Preliminary analysis

Based on the data obtained, the overall temperature stability of the storage area and the registered temperature fluctuations are analysed. The resulting temperature values are compared to the acceptance criteria.

The following should be considered during the overall temperature stability analysis:

the ability of systems that provide an established state of the temperature-controlled environment to maintain the temperature within an acceptable range (if any);

the overall temperature stability of the analysed storage area, as well as the range of temperature fluctuations observed throughout the observations.

When analysing temperature fluctuations, the individual deviations registered by data loggers should be considered;

b) Minimum and maximum temperature, defined hot and cold points

During mapping, temperature fluctuations in the storage area are measured. The data obtained allows the determination of the minimum and maximum temperature values for each data logger, that were registered in the storage area during observations.

Table 2 provides a form for registering the minimum and maximum temperature values, as well as the average temperature values described in subparagraph "c" of this paragraph.

Cold and hot spots are defined to identify the locations of the most preferred sensor location. These spots should be determined for different seasons, since their location and characteristics may vary significantly in winter and in summer.

Additionally, it is important to pay attention not only to maximum and minimum temperature values, but also to overall upward and downward trends to form a prognosis for temperature fluctuations in future;

c) Average temperature values

For each analysed storage area, it is reasonable to determine the arithmetic mean temperature for each data logger. This parameter is most informative for storage locations with periodic temperature fluctuations (sinusoidal fluctuations, or periodic peaks), as well as with fluctuations depending on the location of data loggers.

This parameter can be used to determine the average temperature for each data logger location over the analysis period, and then compare the values to identify locations where the average temperature is steadily higher or lower. A simple comparison of individual values may not be effective in such cases.

Average values can be also used to confirm true hot and cold spots;

d) Interpreting the results and developing recommendations

Data analysis to assess the overall temperature stability of the analysed storage area is recommended to be performed in regard to established acceptance criteria.

Assessment of the overall stability of temperature maintaining in the analysed storage area should be evaluated by considering the maximum and minimum temperature values registered during the observation period.

Factors that explain the observed temperature variations (e.g., location of heating or cooling equipment, or doors) should be described.

The potential impact of consecutive and/or one-time temperature fluctuations and deviations on the security of temperature-sensitive products should be assessed.

Based on temperature fluctuation data at the locations of data loggers, recommended storage areas for temperature-sensitive products should be selected, and the optimal locations for routine temperature monitoring sensors and control sensors should be determined to activate heating and cooling systems for the storage area.

16. Mapping report

A mapping report is the final document based on the results of the analysis of temperature variations in storage areas.

The mapping report should include the following sections:

a) the mapping object (description of the analysed storage area);

b) information about the participants (corporate employees who were involved in the mapping procedure);

c) general information (information on data loggers used, text and schematic descriptions of their location in the storage area, investigation program);

d) acceptance criteria (requirements that the storage area should meet);

e) description of the investigation being conducted;

f) investigation results (calculation of the minimum, maximum and average temperature values; determination of cold and hot spots; establishment of stable storage areas; indication of ambient temperature during mapping in storage areas coming in direct contact with the ambient environment);

g) conclusions and recommendations (a general conclusion describing the suitability of the investigated object for storage of temperature-sensitive products, recommendations and notes);

h) the annexes required (e.g., characteristics of the analysed object with data logger locations;

i) tabulated summary data in an appropriate format (Tables 1 and 2);

j) tabulated data and temperature plots for each data logger used during the mapping, in electronic or hard copy; raw data analysis results, including cold and hot spots; key documents and records generated during the mapping; and deviation reports, including forms to describe corrective and preventive actions;

k) information confirming the metrological suitability of the data loggers used).

Examples of recommendations resulting from the mapping conducted may include, but are not limited to:

a) drawings (diagrams) or information indicating the locations of storage conditions that are not in accordance with the established standards in the analysed area; these should be further excluded from the storage area.

b) proposals to relocate the fixed sensors of the temperature monitoring system within the warehouse area;

c) proposals on regulation (replacement) of equipment that provides the controlled environment conditions;

d) making decisions to change the function of a storage area due to its unsuitability for storing temperature-sensitive products.

The report should be prepared in hard copy and/or as an electronic document and approved by the person responsible for mapping.

Table 1

Location of data loggers

Data logger ID No.	Data logger serial No.*	Diagram No.	Height of data logger location, m	Note

*: to be filled in if the serial No. differs from the ID No.

Table 2

Temperature distribution

Data logger ID No.	Data logger serial No.*	Minimum temperature, °C	Maximum temperature, °C	Average temperature, °C	Compliance with the established range	
					yes	no
Mapping start date and time:						
Mapping completion date and time:						

*: to be filled in if the serial No. differs from the ID No.