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Rationale for the Necessity of Temperature Mapping Of Storage Areas for Pharmaceutical Products

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Abstract

The article is devoted to the issue of ensuring control of one of the main conditions for storage of medicinal products - temperature maintenance in rooms for storing (warehouses). The authors consider approaches to identifying critical temperature points in the storage room and determining the suitability of the given room for storing medicinal products. Taking into account large areas and multi-tier structure of modern storage facilities for pharmaceutical products, maintaining specified temperature range at any point of this volume is a complicated technical task. The objective of the study was to select the best strategy for deciding where to place control devices in the storage room. To solve the task an analysis of temperature control methods was carried out. As a result of the study, general requirements were formulated for the preparation, measurement and processing of data for drafting of isothermal surfaces. Temperature field, drafted after measurements and analysis, allows to choose optimal locations for temperature control devices.

Key words: temperature mapping, temperature field, temperature control for storage of pharmaceutical products

INTRODUCTION

Non-observance of storage conditions is one of the most frequently detected violations during inspections of pharmaceutical warehouses for all subjects of circulation of pharmaceutical products. Furthermore, the most common violation is the deviation from the established temperature storage conditions. Failure to maintain the needed temperature range may cause absence/change of therapeutic action of the product and lead to serious adverse effects on the patient's health.

Modern pharmaceutical products are produced in the course of a complex high-tech manufacturing process, and proper storage conditions (temperature, humidity and other factors) are regulatory requirements for maintaining their quality.

Storage requirements are established in relevant regulatory legal acts and guidelines for manufacturers, wholesale organizations, pharmacies [[1]-[5]]. In addition, WHO Guidance for the Storage and Transport of Time- and Temperature-sensitive Pharmaceutical Products [[6]] sets out general requirements for general requirements for the location of temperature control devices.

This approach without detailed research allows temperature control in small storage areas. However, the compliance with these requirements in conditions of a modern storage facility of a manufacturer or wholesale trade company is insufficient to ensure strict control over the temperature.

Modern storage facilities are characterized by large areas and multi-tier structure, and maintaining specified temperature range at any point of such volume is a complicated technical task. [[11]] This task is especially complicated by the narrow limits of established temperature ranges for storage areas, storage room volume, the amount of racking (shelving) equipment, operating machinery and personnel.

General requirements to storage facilities for medicinal products, described in the WHO Guidance for Qualification of temperature-controlled storage areas [[8]], do not give assurance that the specified temperature range is maintained throughout the whole storage volume. The initial choice of points for the placement of control devices does not always reflect the real distribution of temperature in the room, in addition, the task is complicated by dynamic changes of temperature at each point of storage volume (part of the total volume of storage room, remaining after excluding the volume of components and spaces, recognized as unacceptable for storage).

Thus, it is necessary to justify the placement of control devices in the storage area, so that it can be asserted with a high degree of confidence that the storage temperature of drug products in the entire storage volume will be within the established limits.

MATERIALS AND METHODS

Authors obtained actual material during the audits of storage facilities at pharmaceutical enterprises. Authors studied practical methods of monitoring the temperature in the storage areas, as well as the possibility of ensuring the target temperature regime, using those methods.

RESULTS

To ensure a constant temperature regime in the storage room, it is necessary to answer two main questions:

- In which points of the specified storage volume should we place control devices?
- How often (with what periodicity) should we monitor the readings of control devices?

Normally, a well-formed *temperature field* or *temperature mapping* can help answer these questions. An initial temperature mapping exercise should be carried out on the storage area before use, under representative conditions [[9]].

A temperature field is the set of temperature values at a given moment of time in all points of the studied space.

The general equation of the temperature field is as follows:

$$t = F(x, y, z, \tau)$$

where t – environment temperature;

x, y, z – coordinates of environment points;

τ [tau] – time.

The temperature field can be characterized by *isothermal surfaces* - a geometric locus of points having the same temperature at a given moment. Isothermal surfaces corresponding to different temperatures cannot intersect each other. When isothermal surfaces intersect with a plane, for example, with the drawing plane, they leave traces on this plane in the form of contour sets called isotherms. [[10]]

Temperature field helps to:

– determine in which places of the warehouse and at what height to install temperature sensors;
– determine the required number of sensors for the most accurate control;
– save the budget of the control procedure;
– identify most critical places of storage areas with the risk of non-compliance with storage conditions;
– identify storage areas with the required stable temperature range.

To form isothermal surfaces for the whole storage volume we install a certain number of temperature control devices at different heights with a certain horizontal placement density and take readings with a given periodicity. Practically, to perform this task we should consider a number of issues:

- the required number of levels for control devices installation in a specified storage volume
- the density of placement of control devices at a given level of storage
- periodicity of readings from control devices
- duration of the procedure for taking readings from control devices

There are two approaches to solving these issues.

First. Use WHO guideline for measuring and assessing the microclimate of industrial premises [[11]], which identifies the following:

- *Length and width:*
  - EDLMs (electronic data logging monitors) should be arranged in a grid fashion along the width and length of the area so that the area is reasonably covered, with EDLMs located every 5–10 metres.

- *Height:*

At each point on the grid, arrange EDLMs vertically as follows:

  - If the ceiling height is 3.6 metres or less, position EDLMs directly above one another at high, medium and low level (e.g. one EDLM at floor level, one at 1.2 metres and one EDLM at 3.0 metres.
  - If the ceiling height is greater than 3.6 metres, EDLMs can be arranged in vertical arrays at the bottom, middle (multiple) and top of the space. For instance, for a storage area 6 metres in height, EDLMs can be positioned in each grid location at heights of 0.3 metres, 1.8 metres, 3.6 metres and 5.4 metres.

Second.

One of quite common practical approaches that is often encountered among companies with large amount of retrospective temperature data for the storage area.

Temperature control devices are placed on three levels: the lower, middle and upper storage levels.

Control devices at each level are located at the corners and in the center of the storage volume.

The measurements are taken every 2 minutes during 3-5 days.

A risk-based approach can be used to determine the location of the EDLMs. Consider the following risk factors for the location of temperature sensors: proximity to the doors, operating cooling / heating equipment, other areas, where the greatest variability of temperature is expected based on the experience of warehouse exploitation. The number of control points depends on the size of the room and the diurnal and seasonal variations in temperature. It is necessary to rank raw materials, materials, semi-products and finished products according to the sensitivity to storage conditions and the temperature differential. Such ranking will allow to identify areas that require increased attention to temperature control.

DISCUSSION

Given the described approaches, it is possible to formulate general requirements for the preparation, measurement and data processing in order to draft isothermal surfaces, which characterize the temperature field of the storage volume.

Preparation.

Preparatory actions are an important stage, and inattentive attitude towards them threatens to undermine the multi-day work of the involved personnel.

It is recommended to start with a plan on carrying out temperature mapping, specifying the purpose, specific time limits and a working group including those responsible for the quality of medicinal products, as well as representatives of technical support departments.

It is necessary to hold a meeting of the working group beforehand and discuss the following:

- sequence and scope of performing works;
- placement of control devices on the plan of the investigated storage zone (area);
- documents confirming that the equipment or support systems influencing the room temperature are properly installed, operate correctly and provide the expected results [[12]];
- a list of control devices used for measuring, date of verification, the rules for their placement, installation and removal [[13]];
- distribution of performers for each type of work during the entire period of preparation, measurement and result processing.

When placing control devices, the following requirements should be met:

- Devices must be located by storage zone levels. The number of these levels should be justified either by WHO guideline recommendations [[11]] or by results of similar measurements in the past.
- Try to achieve uniform distribution of temperature control points at the measurement level.
- Place control devices only in anticipated storage volume.
- Begin with placing control devices along the perimeter of measurement levels for which isothermal surfaces are made.
- Provide separate control for the storage volume adjacent to the sources of heat / cold, sensors for automatic activation of equipment or support systems that affect the room temperature.
- Due to the long period of measurement, the control devices should not interfere with the production activity in the investigated storage volume.
- Locations of control devices should be clearly marked and visible to service personnel.

Measurement.

After the beginning of measurement process (switching on control devices to record temperature values at specified time intervals), it is necessary to monitor at least 3 times per day those devices, asking personnel about observed incidents that affect the storage temperature (longtime opening of entrance doors, failure of equipment or support systems affecting temperature in the room, etc.).

Measurement results should be documented in a separate annex to the report on temperature mapping and stored in paper and electronic form.

Data processing.

Measurement results allow drafting of isothermal surfaces for the number of measurement levels with the maximum and minimum values at each measurement point. (Figure 1)

Having drafted isothermal surfaces, we determine "hot" and "cold" areas of the temperature field to place the temperature control devices (Fig. 1 points 1 and 2, respectively).

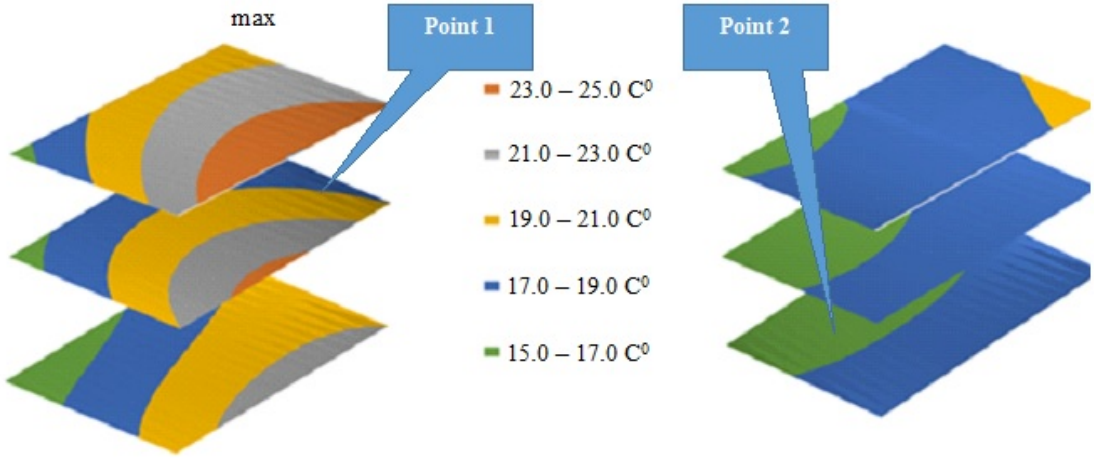

Figure 1. Isothermal surfaces of measurement levels, for maximum and minimum values at each measuring point

These points are used for the installation of control devices to conduct daily (routine) monitoring of storage temperature in a whole storage volume. Having installed control devices in these points, we can assert with a high degree of confidence, that the entire storage volume has a uniform temperature range that does not exceed the range of readings for the "cold" and "hot" storage zones in a given space.

In some cases, isothermal surfaces are not drafted; instead, a set of graphs for the readings of the control devices are built. However, such method of measurements processing makes it difficult to identify several critical areas (if they exist), and makes it impossible to identify storage areas / locations with a risk that the temperature exceeds the range set by the drug manufacturer.

The presence or absence of automated temperature systems in the storage facility influences the periodicity of temperature measurement (to timely register the temperature that exceeds the controlled range).

The measurement periodicity for automated systems should include the moments of their start/stop; moreover, it is necessary to specify reduction of the time interval between temperature measurements when opening the door in a room, abnormal ambient temperature deviations and etc.

In the absence of automated temperature systems, measurements are carried out at least twice a day. Hours with the maximum permissible temperature deviations (temperature extremums) are found from the graph of the average temperature over the entire period of temperature mapping.

Report.

Documentation of results of temperature mapping is an important stage of the whole process. Based on the results of temperature mapping we prepare the document that includes all calculations, diagrams, tables and other data giving a justification for the conclusions. The report should reflect the locations of temperature control devices and the frequency of their verification, which allows with a sufficient degree of confidence to assert that in entire storage volume the temperature does not exceed the limits established by the manufacturer.

It is also necessary to provide recommendations including clarification of the procedure for conducting next temperature mapping, change in frequency of mapping, guidelines for technical services on effective operation of equipment or support systems that affect the temperature in the storage facility and etc.

CONCLUSIONS

Thus, after analyzing the drafted temperature field, it is possible to choose the optimal locations for the control devices. These places are also used to correct (identify) the location for sensors that switch on/off the equipment or support systems that affect the temperature in the storage facility.

It is obvious that the reduction in the number of control devices (which theoretically can be installed in each place of storage of medicinal products) significantly reduces the cost of a temperature control system itself, without affecting the quality of the medicines stored in the given room.

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