Mapping Study Strategies in the Manufacturing Industry

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Abstract *— The following article is focused in strategies to conduct Mapping studies for the manufacturing industries. Mapping studies are used to document and control the distribution of environmental conditions in a determined space. These studies are performed by strategically placing sensors in equally distributed points to identify and eliminate if necessary critical points (cold/hot spots). This article will be focused on good manufacturing practices (GMP) and CFR 210 & 211. Also to present a strategy to the industry on the basics of mapping studies, describe the uses, outline possible study requirements guide. A mapping study was performed in a raw material warehouse. The study consist in monitoring static conditions for one (1) day and at dynamic conditions for seven (7) consecutive days by placing sensors strategically in the warehouse. Environmental conditions were monitored and results were successfully achieved. The maximum temperature and relative humidity recorded during the study was 76°F and 69%, complying with the required specification defined in this article. This means that the raw material warehouse complied with the intended use at the solid dosage pharmaceutical.*

Key Terms – *Mapping Study, Environmental Distribution, Storage of Materials.*

INTRODUCTION

Good storage and distribution practices apply to all organizations and individuals involved in any aspect of storage and distribution of all drug products.

The purpose of a temperature and relative humidity study is to document and control the distribution of environmental conditions in a determined space.

This document describes how to carry out a systematic mapping study in a warehouse for raw materials for a pharmaceutical industry of solid dosage. Manufacturing facilities use warehouses to store raw materials that will be converted into finished goods. These materials must be kept in safety and good care. The timeframe of storage can be short period or longer depending upon nature and requirement of materials.

Any damage or theft to the materials is going to increase cost to the organization. So it becomes important for the organization to have a robust and effective warehouse as well as materials management.

BACKGROUND INFORMATION

A mapping study establishes the temperature distribution within the zone being mapped and it locates hot and cold spots. The collected data provides an essential source of information to ensure that all time and temperature sensitive pharmaceutical product are correctly stored within their temperature ranges. Mapping also identify zones where remedial action needs to be taken; for example by altering existing air distribution to eliminate hot and cold spots, or by altering existing air distribution to eliminate hot and cold spots, or by retro-fitting new air distribution equipment to reduce temperature.

A temperature mapping exercise involves a four stage process, as follows:

- Prepare a mapping protocol.
- Carry out the mapping exercise.
- Prepare a mapping report.
- Implement the recommendations by carrying out the remedial and other actions identified in the mapping report. A follow-up mapping exercise may then be needed to verify the effectiveness of the remedial actions [1].

A mapping operation requires a sufficient number of Electronic Data Logging Monitors (EDLMs) to ensure that the temperature distribution in the space to be mapped is adequately characterized. In addition, suitable computer equipment and software is needed to store and analyze the data. The selected EDLMs must:

- Be technically suitable for the specific mapping task and for the intended operating environment.
- Provide a reliable and continuous reliable record of time-temperature data.
- Have an appropriate temperature range so that all anticipated temperature extremes can be recorded.
- Have a user-programmable data sampling period, with time intervals raging from one (1) minute to fifteen (15) minutes or more sufficient memory for the intended length of the study and the chosen recording interval.
- Have a NIST-traceable 3 point calibration certificate with guaranteed error of no more than ± 2.5°F to each calibration point.
- Allow the recorded time-temperature data to be downloaded to a computer system for subsequent analysis.
- Have data storage and analytical software that complies with the applicable regulatory requirements (21 CFR part 11).

As part of a mapping study, the following risks should be considered:

- Goods stored close to the loading may be affected by drafts.
- Goods stored near the north-facing wall and window may be affected by solar heat.
- Lights can be source of heat. Goods placed on high racking in close proximity to a light may be at risk.
- Goods movement and other activity in the more trafficable areas of the warehouse is likely to cause drafts.
- Good stored on tall racking is likely to have wide temperature variation from top to bottom [2].

When determining the sensors locations, it is important to document a rationale for choosing the locations, as well as create a diagram that provides a visual map of the locations. It is essential that every sensor be accurately identified by a unique ID number and a defined location.

With regards to determining the number of sensors appropriate for your temperature mapping effort, there is not set formula. Guidelines suggest placing sensors uniformly throughout all three dimensions of the storage area. The number of sensors used must be enough to provide an accurate assessment of temperature distribution in the area.

If the product is sensitive to relative humidity, it is necessary to use loggers that will record both the temperature and relative humidity in the monitoring locations of the storage area. For humidity mapping studies, the number of humidity loggers to be placed is typically fewer than the number of temperature loggers. These loggers are placed in areas of higher risk.

The results of the mapping exercise must be analyzed and compared against the acceptance criteria as defined in the qualification protocol. From the data, the analyst can identify critical areas where the stored product may potentially be exposed to unacceptable temperature and humidity conditions. With this information, you can analyze if alterations are needed to counteract the extremities. This may include making changes to the HVAC system, re-positioning sensors, or relocating shelves to a modified design. Depending on the alterations proposed, an additional mapping study may be necessary to identify the new environmental profile and consequently the correct location of the monitoring sensors.

The mapping process will help determine when excursions could occur and are useful when pharmaceuticals manufacturers develop a plan for dealing them. Alarms should be used to reveal environmental excursions during operations. Temperature excursions for brief periods outside of a storage label conditions may be acceptable provided stability data and scientific/technical

justification exists demonstrating that product quality is not affected [3].

The mean kinetic temperature (MKT) is the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of all the individual degradations that would occur at various temperatures. MKT may be considered as an isothermal storage temperature that simulates the non-isothermal effects of storage variation [4].

The temperatures used for calculating MKT can be conveniently collected using electronic devices that measures at frequent intervals. MKT can be calculated directly or the data can be downloaded to a computer for processing [5].

The holding of a drug may occur as part of storage and distribution practices. Drug products in the distribution chain may be held at temperatures outside their labeled storage requirements as determined by an appropriate stability study. Drug products stored either in warehouse conditions or in transportation modes may experience excursions from their environmental ranges... Each product excursion must be evaluated to determine the final product effect. The means of the evaluation must be scientifically sound with documented technical justification that the integrity of the drug product has not been affected. One method of analysis for drug product is the use of an MKT calculation. The MKT express the cumulative thermal stress a product experiences, it is considered an acceptable practice storage and it follows that it should be considered for transit excursions in the process distribution. The calculation must be justified for use with distribution excursions by confirming that the stability limit characteristic of the product follows first order kinetics over the temperature range encountered [5].

METHODOLOGY

This section provides a detailed plan of how the research will be performed. Data will be generated and analyzed to demonstrate that the raw material warehouse complies the environmental requirements, assuring excipients will not be impacted.

The temperature and relative humidity study will be performed during one (1) day in static conditions and seven (7) consecutive days in dynamic conditions to represent "worst case" scenario in accordance to the industry practices. The dynamic conditions will consider an evaluation of normal operations including personnel, equipment movement, material movement and opening/closing doors to represent the traffic and level of activities normally occurring in the warehouse.

Temperature and humidity readings will monitor the conditions at intervals of 15 minutes. The amount of samples generated will constitute a database representative of the normal conditions in the warehouse and the quantity will be statistically appropriate to demonstrate the applicable models exhibited throughout the profile.

The distribution of the data loggers inside the warehouse is equally distributed point following the example the technical guidance document related to a solid dosage pharmaceutical.

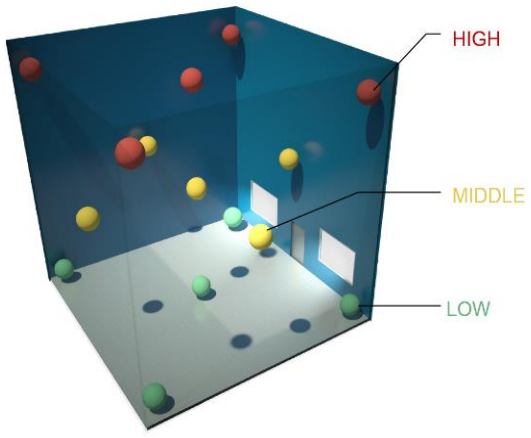

Figure 1
Equally Distributed Points Example

The quantity of data loggers is determined based on the warehouse total volume and applicable considerations including quantity of levels, facility design and ventilation/cooling systems. The total quantity of data loggers is calculated to comply

with the minimum number defined in accordance to a procedure related to a solid dosage pharmaceutical. Refer to Table 1 for sensors (data loggers) quantity per cubic meter.

Table 1
Sensor Quantity per m³

Sensor Quantity per m^3		
Warehouse Volume (m^3)	**Incremental Number of Sensors**	**Total Number of Sensors (*)**
<100	---	10
100 - 500	---	15
500-1000	---	16
1000-10000	1 per 1000 m^3 increment (and partial) above 1000 m^3	16-25
>10000	1 per 5000 m^3 increment (and partial) above 10000 m^3	no less than 25

In addition, there should be one sensor placed outside the warehouse and a defined number of sensor at hotspots and cold spots in the warehouse.

To determine the minimum of sampling points to be installed in the warehouse of raw materials it was calculated the volume using (1):

Volume = (length) (width) (height) (1)

The warehouse total volume is approximately 188m³. The amount of sensors per above calculation shall be established at a minimum of fourteen (14). Three (2) additional sensors placed outside the warehouse at hot and cold spots of the warehouse.

All sensors / data loggers placed warehouse will monitor temperature and relative humidity conditions across the area and will be evaluated. The evaluation of the sensors reports will be performed to document maximum and minimum values.

The required temperature and relative humidity specifications is defined in Table 2.

Table 2
Temperature and Relative Humidity Specifications

Warehouse Environmental Specifications		
Area	**Temperature**	**Relative Humidity**
	Limit	**Limit**
Warehouse	NMT 80°F	NMT 70%

For the distribution of the sensors, refer to Figure 1.

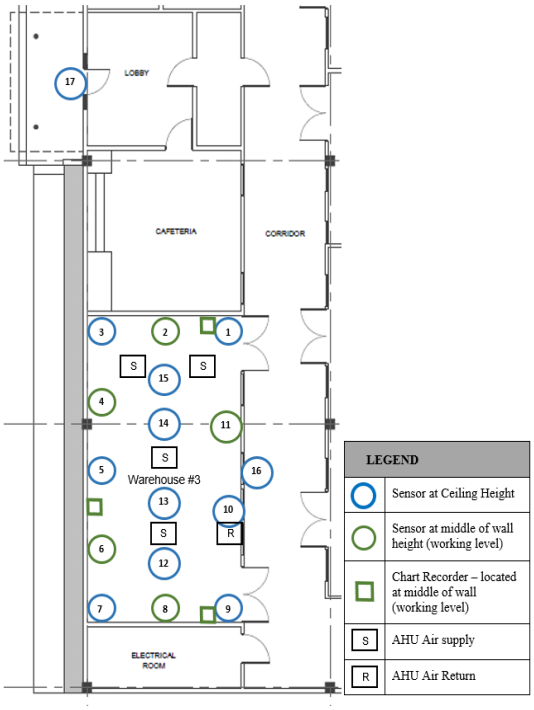

Figure 2
Sensor Distribution Diagram

RESULTS AND DISCUSSION

This section includes the results obtained during the temperature and relative humidity monitoring study. Temperature and humidity recorders demonstrated that the warehouse complied with the requirements of the solid dosage pharmaceutical. These were proved by monitoring one (1) day at static conditions and seven (7) consecutive days in dynamic conditions. Calibrated data loggers were placed in representative and worst case locations in order to verify the corresponding room parameters. Refer to Figure 1 (Distribution of Sensors for data logger locations.

Maximum and minimum values were recorded at static conditions and documented in Table 3.

Table 3
Temperature and Relative Humidity Readings for Static Conditions

Temperature and Relative Humidity Max. & Min. Values				
Sensor	Temperature (°F)		Relative Humidity (%)	
	Actual Max.	Actual Min.	Actual Max.	Actual Min
1	70.293	66.992	65.901	58.742
2	20.165	66.436	67.360	60.431
3	72.315	67.933	64.682	55.879
4	N/R	N/R	N/R	N/R
5	74.865	70.293	61.502	53.299
6	75.256	69.564	59.742	49.860
7	74.952	70.680	60.134	52.541
8	73.006	69.177	61.897	54.432
9	72.144	68.578	63.604	56.406
10	71.541	67.892	64.370	56.970
11	70.637	67.806	64.775	58.584
12	71.497	67.591	65.241	57.702
13	73.308	69.177	62.543	55.083
14	73.006	68.448	62.566	54.044
15	73.006	68.320	63.880	56.056
16	71.884	67.678	64.836	57.115
17	87.633	75.342	84.933	55.987

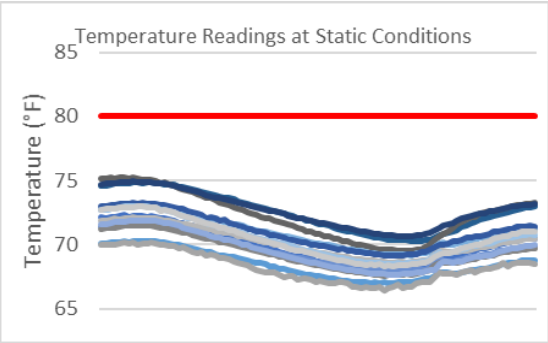

Figure 3
Temperature Readings at Static Conditions

The mapping study for the static conditions was performed during one (1) day. Data loggers were turned off and removed from the warehouse. The data was downloaded to start the analyzing process. The analysis of data consisted in finding maximum and minimum values and generate graphs. The observed behaviors of temperature and humidity per condition. After analyzing data for the warehouse, all data loggers recorded temperature values that complies with the temperature requirements of no more than 80°F established in Table 2. Data logger number six (6) recorded the maximum value of 75 °F. Data logger number sixteen (16) and seventeen (17) recorded external conditions for reference. Refer to Figure 3 for the behavior of temperature during the dynamic conditions.

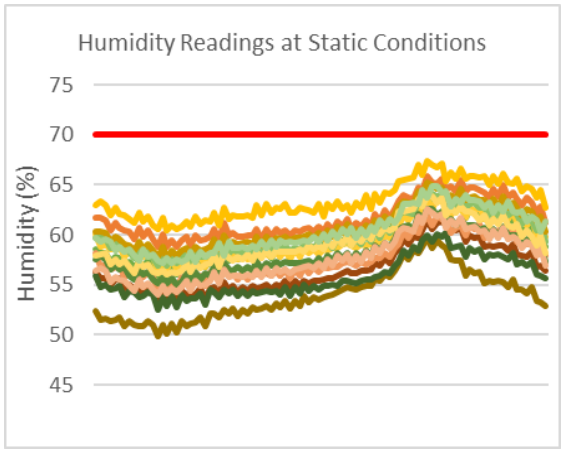

Figure 4
Relative Humidity Readings at Static Conditions

All data loggers located at the warehouse complied with the relative humidity specification of no more than 70%. Refer to Figure 4 for the relative humidity behavior during the static conditions.

Maximum and minimum values were recorded at dynamic conditions and documented in Table 4.

Table 4
Temperature and Humidity at Dynamic Conditions

Temperature and Relative Humidity Max. & Min. Values				
Sensor	Temperature (°F)		Relative Humidity (%)	
	Actual Max.	Actual Min.	Actual Max.	Actual Min
1	71.928	66.906	67.459	56.044
2	72.271	66.821	66.700	55.047
3	75.951	68.362	66.231	48.458
4	75.429	69.177	63.180	49.282
5	76.123	69.993	64.199	50.529
6	77.212	71.024	61.087	47.134

7	76.298	70.981	60.870	48.063
8	75.646	70.637	60.938	49.577
9	76.341	73.006	56.117	50.244
10	72.617	67.849	64.432	53.284
11	72.517	67.464	66.632	54.630
12	71.110	65.707	67.137	55.329
13	68.063	62.154	75.758	65.075
14	73.667	68.106	65.831	53.291
15	73.567	64.638	69.101	58.593
16	69.993	65.123	68.361	54.643
17	89.100	76.210	95.256	53.810

The mapping study for the dynamic conditions was performed during seven (7) consecutive days. Data loggers were turned off and removed from the warehouse. The data was downloaded to start the analyzing process. The analysis of data consisted in finding maximum and minimum values and generate graphs. The observed behaviors of temperature and humidity per condition (static or dynamic). After analyzing data for the warehouse, all data loggers recorded temperature values that complies with the temperature requirements of no more than 80°F established in Table 2. Data logger number nine (9) recorded the maximum value of 76 °F. Data logger number sixteen (16) and seventeen (17) recorded external conditions for reference. Refer to Figure 5 for the behavior of temperature during the dynamic conditions.

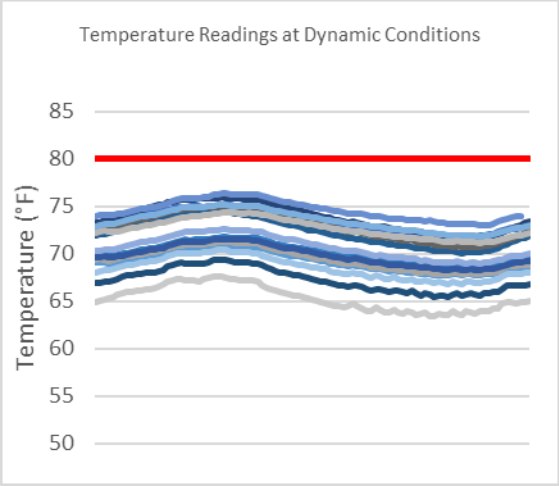

Figure 5
Temperature Readings at Dynamic Conditions

All data loggers located at the warehouse complied with the relative humidity specification of no more than 70% with exception to data logger number thirteen (13). After investigating the area in which the data logger was located, a leakage was found from the ventilation duct located above the point. This was informed to the Utilities Department and repaired the leakage of the duct. This situation is considered isolated since the rest of data loggers and chart recorders met the established acceptance criteria. This does not impact the product stored. The rest of the remaining locations were not impacted by the leakage. Therefore, the warehouse is acceptable for its intended use. Refer to Figure 6 for the relative humidity behavior during the dynamic conditions.

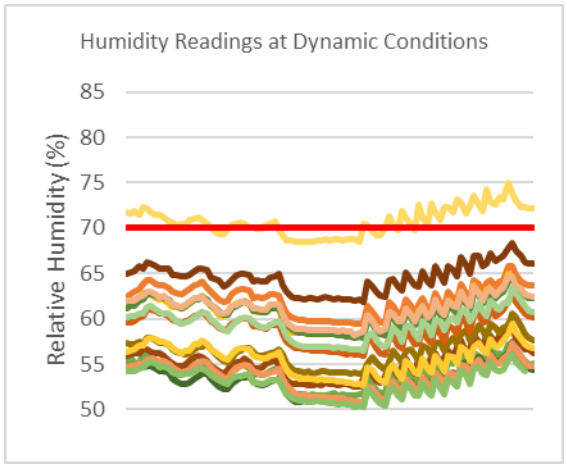

Figure 6
Humidity Readings at Dynamic Conditions

The mapping process helped to determine excursions. Temperature excursions for brief periods outside of a storage label conditions may be acceptable by providing stability data and scientific and/or technical justification demonstrating that product quality is not affected.

CONCLUSION

The objective of this article was successfully achieved following the methodology. All temperature and relative humidity readings were within the specified limits. The practices and processes set in this article apply to storage of the life-cycle management of drug products. All

involved should ensure the product to its point of use, creating a contiguous supply network that is collaborative and emphasizes preventive measures to protect drug quality. Any damage or theft to the materials is going to increase cost to the organization. So it becomes important for the organization to have a robust and effective warehouse as well as materials management

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