Temperature Mapping at a Pharmaceutical Product Warehouse

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Abstract - To sustain pharmaceuticals products with high quality until they arrive to the patients, it is necessary to store them under specified temperature conditions. Warehouses that store these kinds of products use temperature sensors that collects data seven days a week, 24 hours a day, to ensure that an excursion is not happened. Is a requirement of the United States Food and Drug Administration (FDA). To validate those sensors, a temperature mapping must be performed. The temperature mapping is a tool, which involves temperature loggers that are placed strategically, to monitor a controlled enviroment. If a temperature value is not under the established range, it is considered a temperature excursion. In this study, a temperature mapping was executed to determine if there is a temperature excursion on a pharmaceutical product warehouse. After this study, the collected data by the temperature mapping will be used to validate the established sensors.

INTRODUCTION

To maintain pharmaceutical products until they arrive to the patients, warehouses that storage them must control their conditions to the required parameters. Because of that, any space that is used to storage and handle products with a specified labelled storage temperature must do a temperature mapping, especially when those products are medical device, generic drugs, and over-the-counter pharmaceuticals [1].

Temperature Mapping

Temperature mapping can be defined as the process of mapping the changes in temperature that occurs within a single temperature-controlled system [2]. Those changes can be consequence of opening doors, cooling fans at short distance, movement of personnel, and quantity of products that are stored at a specific time. The temperature mapping is used to locate the points of greatest temperature fluctuation. Then, these fluctuations are analyzed to find the causes. Also, it can be used to create the worst-case scenario with the intention of verifying if the system maintains the correct temperature in any situation cause by influence of an external factors, as of the weather, and/or internal factors, as of airflow restriction on the air condition system. The differences in temperature are studied to make sure that the system consistently meets the company standards.

In controlled rooms, the temperature between spaces can vary up to 10°C (50°) [2]. Typically, the center of the room will maintain the most constant temperature. The corners and surroundings areas can fluctuate. The importance of the temperature mapping in the organization helps to deal with the temperature sensitive products, like medications and vaccines. Temperature mapping always allows to verify that the warehouse maintain an acceptable temperature at each rack for those products. This data is used to support the ongoing use of monitoring systems. Once these points of temperature variation are found using the temperature mapping, a monitor system can be installed, so the company and users can have the data to comply with the standards.

Temperature Excursion

Temperature excursion are defined by the World Health Organization (WHO) Model Guidance as "an excursion event in which a Time Temperature Sensitive Pharmaceutical Product (TTSPP) is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different' they are determined by the product manufacturer, based on stability data" [1, 3]. If a temperature excursion occurs during storage or transportation, it should be reproted to the distributor and recipient of the affected pharmaceutical product. A procedure should be taking place for investigating and handling temperature excursions.

Pharmaceuticals manufactu-

Figure 1 - Mofongo Burger

rers has the responsibility to deliver the medical products with the right quality attributes. Control the storage and transport conditions of pharmaceutical prodcuts until they arrive to the patient is one key element in achieving a high-quality product. It is usual for the storage to experience uncontrolled situations in where the temperature is not or deviates of the speficify value. For medicines, that are temperature sensitive products, one possible consequence can be temperature excursions (when the temperature range is exceeded). Temperature excursion can be difficult to handle when there is often no way to precise the next condition that the product will be exposed to, for example when a natural disaster or human-related event occurs.

Prescription Drug Marketing Act of 1987

The Prescription Drug Marketing Act (PDMA) of 1987 is a federal law signed by the President of the United States, Ronald Reagan, on April 22, 1988. With this act, the United States federal government can ban the reimportation of drugs produced in the country, place restrictions on the distribution of drug samples, and ban certain resales of drugs by hospitals and other health care entities [4]. The PDMA was enacted:

- To ensure that drugs product delivered to the customers are safe and effective;
- To avoid the unacceptable risk of consume drugs that are counterfeit, adulterated, misbranded, subpotent, or expired.

The PDMA was necessary to increase safeguards in the drugs distribution system. It prevents the introduction of a retail sale of substandard, ineffective, or counterfeit drugs. This act regulates the way in which the company store the pharmaceutical products and medical devices. The PDMA of 1987 was then modified to the Prescription Drug Amendments of 1992. This modified document said that the company has the obligation of storing the drug products in conditions where they don't lose their stability, integrity, and effectiviness.

If a company that distributes pharmaceuticals products doesn't comply with the PDMA regulations, they can be exposed to penalties. Those penalties can be consider as felonies or misdemeanors. If it is consider as a misdemeanor the people involved will be punished by prison of not more than one year, a fine of not more than $1,000, or both. If the violation persists, the punishment will be prision of not more than three years, a fine of not more than $10,000, or both. But, the FDA stated that: "most of the PDMA violations are felonies that are punishable by a prison term of not more than 10 years, a fine of not more than $250,000, or both" [5]. A felony is a crime that is severe enough to be punishable by sentences ranging from imprisonment for more than a year, life imprisonment without parelone, and even death [6]. The misdemeanors are less severe than the felonies and they can be consider as administrative infractions and regulatory offences.

If the report of the temperature at the warehouse (including the temperature mapping) is not presented to the FDA, that can be consider as a misdemeanor, but, if this report was not realized, that can be consider as a felony because there is no evidence that the product is safe and effective to be received by the customers.

BACKGROUND

The quality of the pharmaceuticals products depends, largely, upon the environment controls when they are storage and handle [7]. Every pharmaceutical product must be handled and stored under specified storage conditions. That specified storage conditions are labelled on the product information data sheet or product pack. The most important environmental parameter that can impact quality of pharmaceutical product is temperature. If the temperature is not controlled, an excursion can occur with an adverse impact on product quality.

The temperature mapping is essential to maintain the integrity and quality of temperature sensitive product. This process allows products, merchandise, and items to meet the government and company requirements. With this process, the company can determine the actual temperature in a tridementional space and assure that is within the range for the products stored [8].

Medical devices and medicines should be stored and transported under control conditions to assure that their quality is maintained. All manufacturers recommend a temperature range were their products should be placed and this involve the use of specialized storage and transport facilities. Temperature sensors are established around the warehouse to monitor the temperature that is released by the air conditioners units with the purpose of maintain a specialized storage facility. Those sensors used are important because they demonstrate compliance with the designated ranges by the manufacturers and assure a product with high quality. They measure the temperature within the warehouse 24 hours a day, seven days

a week at a predetermined interval of time. It is required that storage areas for medicines must be sustained within acceptable temperature limits. Special storage conditions are specified by every manufacture that the warehouse has [9].

In this study, a temperature mapping is performed to assure that temperature sensors are collecting the data within the range of controlled room temperature 68°F to 77°F (20°C to 25°C). The temperature mapping contributes to validate, measuring, and monitor the temperature sensors used by the company. Temperature mapping sensors were calibrated and checked at the controlled temperature range to assure that the collected data is real. Pharmaceutical products should not be subject to unacceptable degrees of heat and cold, because if that occurs, the product must be collocated on quarantine to evaluate their quality. If these products are exposed to temperature out of limit range for an long period of time, they must be discarded and the manufacturers must be notified. Once these medical products have been stored in good conditions, they must be transported to the patients in the same way.

PROBLEM AND OBJECTIVE

A pharmaceutical product warehouse wants to implement a temperature mapping at all his storage area to comply with the United States Food and Drugs Administration regulation. This regulation, knowns as the PDMA, says that every pharmaceutical product must be store in conditions in were their efficancy and safetyness are not compromised. A temperature mapping was realized, taking into consideration their new storage area, to validate the six sensors used to monitor the temperature at every moment. The warehouse counts with 3,775,680 cubic feet that is used for products under the controlled room conditions (air conditioners units maintains the temperature between 68°F to 77°F). Before this temperature mapping, there wasn't one performed because they only applied this method to their freezers (units in where the temperature is controlled thermostatically between -4°F to +14°F).

After the completion of this study, the collected data are going to be used to have a report of the temperature at the warehouse. That report will be used to demonstrate that the company comply with the FDA regulations and that the temperature excursions were verified and corrected. The temperature mapping will validate that the data collected daily are accurate. Also, the sensors validation with the temperature mapping is going to be used by the management of the company to search for new customer, demostrating to them that the controls they have to monitor the conditions of the warehouse sustain the products with high quality until they be deliver to the patients.

RESEARCH METHODOLOGY

The following steps explains the process used to conduct the temperature mapping study at a warehouse.

Step 1 - Temperature Mapping Sensors Selection

The sensors used for the temperature mapping were TempTale®Ultra. They were selected because they have the enough memory for the study's duration and time interval. Those sensors were calibrated wihtin the year interval. The calibration used complies with the temperature range of this study. The calibration principal was: one calibration point below the low end of the range, one calibration above the high end of the range, and one calibration point in the middle of the range.

For this study, two types of sensors were used because of their disponibility. One that measure the temperature and humidity and the other type how measure only the temperature. This doesn't affects the consistency of the study because only the temperature was consider.

Step 2 - Temperature Mapping Team

Many functional teams participated in this study: quality department, engineering department, operations, and the management of the company. The quality department were the ones in charge of audit the process. They ensure that the monitor sensors of the company and temperature mapping sensors used for the study complies with the yearly calibration. Also, they verify that the air conditioners units have the monthly maintenance. The engineering department monitors the temperatures of the air conditioners units throughout six sensors at the warehouse. They verified if a temperature excursion occurs, gave recommendations, and implemented the changes to avoid them. The operations department are the ones who help in the installation and remotion of the temperature mapping sensors. Due to requirement of the company per Standard Operating Procedure (SOP), the temperature mapping must be performed without any personnel or movement of materials on the storage area. Becau-

se of that, the management is in charge of selecting the day of the study's execution. Weekends are commonly used because there is no material distribution.

Step 3 - Acceptance Criteria

The acceptance criteria was determined by the manufacturers of the products. They recommend specific temperatures conditions to sustain the quality of the products. These conditions needs to be keeped at every moment until they arrives to the patients. In this study, the acceptance criteria was given by the controlled room temperature conditions 68°F to 77°F (20°C to 25°C).

The time used to measure the temperature was determined by the company's Standard Operating Procedure that has as requirement of 24 hours (at 15 minutes interval) without movement of material or personnel on the study's area.

Step 4 - Sensors Locations

As per company's Standard Operating Procedure and, because of the magnitude of the warehouse that has 3,775,680 cubic feet, it were required 28 TempTale®Ultra sensors to perform the temperature mapping. It were placed at high, medium, and low distance, taking in consideration the warehouse's racks that are used to store the products.

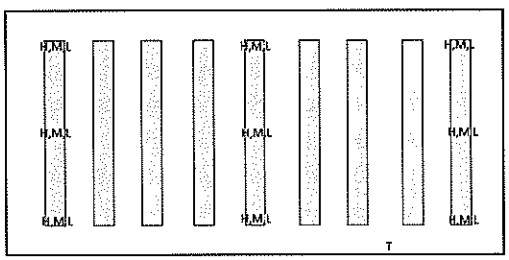

Figure 1 - Locations of the Sensors

At the figure above, the sensors were located at H (which means high), M (which means medium), and L (which means low) distance from the used area to store product. There were three sensors in each corner, three sensors between the corners, and three sensors in the middle. Also, one sensor was placed near a thermostat (represented on the Figure 1 as T). The thermostat are those temperature sensors used by the company to control the air flow released by the air conditioners units. This is with the intention to form an "X". With that configuration, all the warehouse was covered by range of the temperature mapping sensors.

Step 5 - Program the Sensors

The program used to configure the TempTale®Ultra sensors (sensors used to perform the temperature mapping) was Sensitech. With Sensitech, the sensors were configure to start at March 23, 2019 at 8:00 am and ended at Monday, March 25, 2019 when the stop button was pushed. For this study, due to the company's Standard Operating Procedures, only 24 hours of the collected data was consider for the temperature mapping. The first 30 minutes of data were not used for the study because that is the time that the sensors takes to stabilized. Also, the TempTale®Ultra were configured to record the temperature in Fahrenheit.

Temperature sensors were called by the company's building number and an assigned number. In this study, the building is called building 3, so that number is the first to appears. An example of this is: Building 3 Sensor 1 or abbreviated B3S1.

Step 6 - Put the Sensors in Place

The height of the warehouse is 38 feet. Based in that height, the 28 TempTale®Ultra were collocated approximately as low = 12.6 feet, medium = 25.2 feet, and high = 37.8 feet. There were some consideration evaluated to establish the sensors:

- The layout of the area. For example: whether is a square or includes alcoves.
- Product's packages must not block the air flow so that the sensors can read the real temperature.
- Where the products are placed. The sensors must be placed on or near the locations where the products are stored or planned to be stored.
- A place where the sensors not be smashed and/or damaged.

Step 7 - Conduct the Mapping

The temperature was run for 24 hours at 15 minutes intervals. No personnel or movement of material has been allowed on the study area. Once the time passed, the sensors were collected. The serial numbers and locations were double-checked against the installation notes.

Step 8 - Download the Collected Data

The downloaded data was collected using the Sensitech program. Each value was analyzed to intentify temperature excursions.

RESULTS AND DISCUSSION

The size of the warehouse was 3.7 million cubic feet. As per company SOP and taking in consideration the warehouse dimentions, the quantity of TempTale®Ultra needed to perform the temperature mapping were of 28. Those 28 sensors were installed around and in the middle of the warehouse. The building used was known as building 3 and it was previously

Figure 6 - GPS View 1

Figure 7- GPS View 1

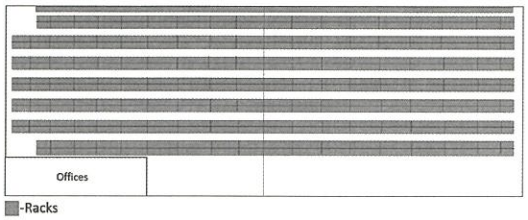

Figure 2 - Warehouse Architectural Plan that Shows the Rack's Distribution

selected by the company to have a temperature mapping.

The Figure 2 shows an example of the distribution for racks on these building. It is important the product storage rack's shape because the sensors must be placed in where they can obtain the real temperature's quantity. The temperature in all the area in where the product is stored is controlled by air conditioners units.

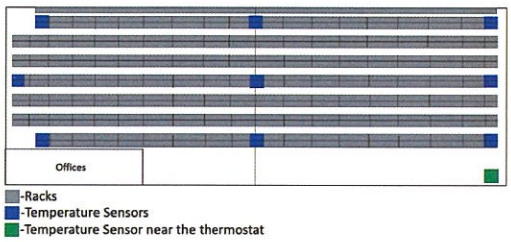

Figure 3 - Warehouse Architectural Plan that Shows in Where the 28 Temperature Sensors Where Installed

The 28 TempTale®Ultra sensors used to perform the temperature mapping were placed forming a "X" figure to cover all the warehouse' area. Sensors were installed in the highest point for potential product storage, in the middle of the product storage area, and at the lowest product storage position. The Figure 3 shows were each sensor were installed. Each blue box on the figure represents 3 sensors installed at high, medium, and low distance from the product storage area. The green box represents only one sensor that was installed near the thermostat. The thermostat are sensors that measure the temperature at all time. That temperature is controlled by the air conditioners units on the building. Building 3 has 6 of them around the warehouse, but as per SOP it was needed just one to be selected to have a temperature mapping sensor.

Once sensors were in place, they started to record the temperature's lecture at 8:00 am on Satuday, March 23, 2019 and they stopped record on Monday, March 25, 2019 when the stop button was pressed. For this study, only 24 hours were taken into consideration as per the company SOP. The temperature mapping was performed on a weekend because it is a company requirement that there is no activity or people present when the sensors starts to measure the temperature until the end of the 24.5 hours. Those 0.5 hours of measurement was because the first 30 minutes are a requirement time that the sensors need to stabilizate. The only time that was took in consideration were between Saturday, March 23, 2019 at 8:30 am until Sunday, March 24, 2019 at 8:30 am.

Figure 4 - TempTale®Ultra Sensors in Where the Temperature Excursions were Found

Is was detected that temperature excursions occurs during the temperature mapping time. Sensors B3S16, B3S17, B3S18, B3S19, B3S20, and B3S21 were indetify with the temperature excursions, as showed on Figure 4. Because the exact location on the warehouse was documented during their installation, it was easy to identify in where the temperature excursions occurs.

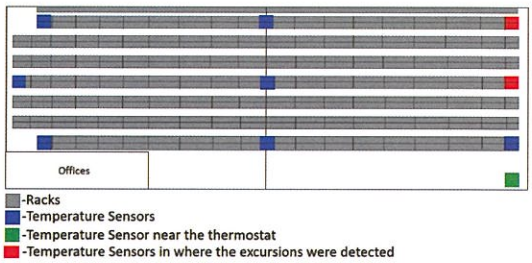

Figure 5 - Warehouse Architectural Plan that Shows in Where the Temperature Excursions were Found

It was discovered that all of the six sensors in where the temperature excursions were identified, were installed on the same location at the warehouse. Figure 5 shows the location in where the temperature excursion were detected.

During the investigation, the area in where the temperature excursions were detected was a project in where the warehouse was extended to storage more pharmaceutical products. Also, a new air conditioner unit was installed to control the temperature on that new warehouse extension. Figure 6 shows the locations of the air conditioners units, including the one in where the temperature excursions were detected.

Regardless the temperature excursions, it can be said that the process is out of control. Figure 7 shows a control chart of the average measured by the temperature mapping. The process is out of control because the first eight

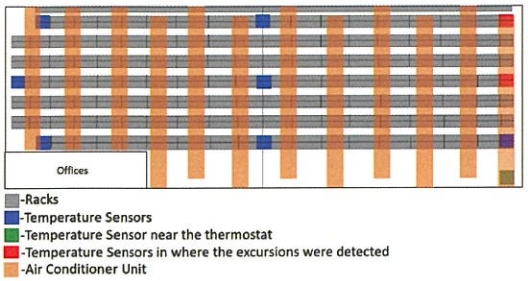

Figure 6 - Warehouse Architectural Plan that Shows in Where the Temperature Excursions were Found

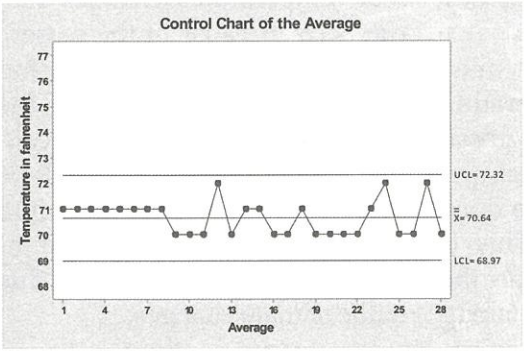

Figure 7 - Control Chart Using the Average of the Temperatures Collected by the 28 Temperature Mapping Sensors

averages are on the same side of the centerline. The cause of this is due to the absent of oscillation on the air conditioner units. If that oscillation doesn't occur, it can freeze the motor causing a damage to the unit. To increase the oscillation of temperature's values, it can increase the range of the controlled value by the air conditioners from 75° on the morning and 72°F for the evening and night. That change in parameters comply with the controlled room temperature range.

After the Temperature Mapping

With the information of where the temperature mapping occurred, the parameters of the air conditioner above were verified. The air conditioner unit on the top of the sensors in where the temperature exclusions appeared has a set point of 72°F, but it was set to control to 70°F. This controlled temperature was changed to 73°F from 12:00 am to 5:00 am, 72°F from 5:01 am to 8:00 am, 70°F from 8:01 am to 7:00 pm, and 73°F from 7:01 pm to 11:59 pm.

Figure 8 shows the program that is used to schedule the temperature of the air conditioner units and the temperature that was placed to prove if the temperature excursion still occurs. These changes were investigated by installing only nine temperature sensors on the place in which the past temperature excursions were found.

Figure 9 shows in where the nine sensors were installed after the parameters of control of the air conditioner unit changed. Those nine sensors were installed in high, medium, and low position on the racks.

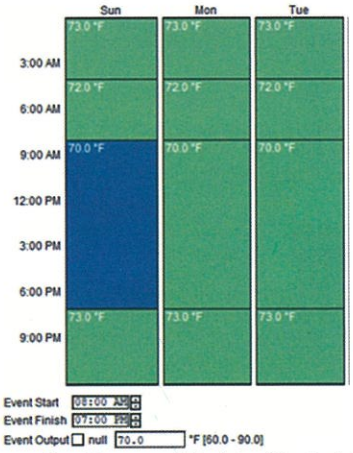

Figure 8 - Program Used to Control the Warehouse's Temperature Through the Air Conditioners Units

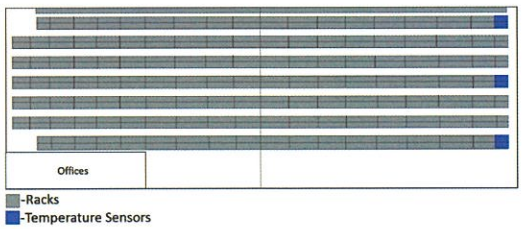

Figure 9 - Warehouse Architectural Plan that Shows in Where the 9 Temperature Mapping were Installed

The only air conditioners unit that was affected by the change in parameters was the one above the temperature excursions, as showed on the Figure 10 (next page). The air conditioner unit was a new one implemented to provide the temperature of the new storage area.

The 9 TempTale®Ultra were set to start measure the temperature between 8:30pm on Saturday, April 6, 2019 to 8:30pm on Sunday, April 7, 2019. Each of these sensors were used to prove if the changes in the control parameters was effective. No temperature excursion was found in those nine sensors.

FUTURE WORK

Because temperature excursions were found during the temperature mapping, it must be repeated on the entire warehouse, with the intention of assure that the implemented changes helped that the problem don't persist.

Once finished the temperature mapping, that uses all of the TempTale®Ultra sensors avaliable at the company, at building 3 a new temperature mapping will be performed on another building. That building is known by the company as building 1 and is, also, used to storage pharmaceutical products. The only difference between both is that building 1 has freezers on the center, that has their own temperature mapping. The freezers temperature mapping were previously performed.

CONCLUSION

To perform this study, it was necessary a coordination between multidisciplinary departments for his success. Due to company

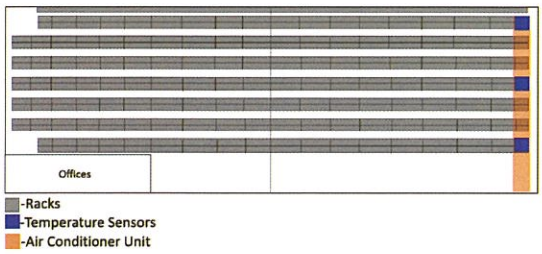

Figure 10 - Warehouse Architectural Plan that Shows the Air Conditioner Unit that is Above the Temperature Sensors

requirements per Standard Operating Procedures (SOP), the warehouse in where the temperature mapping was performed was clear of personnel and movement of materials. This requirement difficulted the study due to the necessity of the business to operate on that Saturday. At the end, it was not required to work on that day. For the next temperature mapping, the perfect time to be executed is between 8:00pm on Saturday to 8:00am on Sunday. On that time, it was comfortable to realize the study because there is not a necessity to distribute pharmaceutical product during that day and neither on those hours.

Other recommendation must be to perform the temperature mapping and increase the possibilities of occurence of a temperature excursions; it can be done during working hours. This is with the intention to evaluate the temperature conditions by taking in consideration the worst scenario. The worst scenario for the sustainability of the ideal's temperature condition for the storage of pharmaceutical products is when doors are constantly opening and closing, and the building has personnel moving those materials at the area.

This study can be also performed two times a year. This is to take in consideration the different temperatures changes that can occur because of the season. With two temperature mapping performed during a the year, the parameters in which the air conditioners must be placed will be more accurate. It will take into consideration the lowering or increasing of the temperature, due to the climate changes.

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