Qualification of the Cold Chain System in Drug Logistics

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Abstract *— Distributions Centers for pharmaceutical products have experienced significant changes in recent years in terms of the cold chain, adapting to new social, economic, and technological structures. The main objective of this process is to maintain a constant cold temperature of refrigerated pharmaceutical products, which requires maintaining a refrigeration specification of 2°C to 8°C. This article aims to use DMAIC tools to help us ensure that deliveries from more distant routes to different customers consistently meet the required temperatures from their departure from the distribution center to delivery to the customer.*

Key Terms *— Cold Chain System, Distribution Centers, DMAIC Method, Pharmaceutical Products.*

PROBLEM STATEMENT

The distribution center in Caguas plays a crucial role in supplying medications, vaccines, and pharmaceutical products to clinics, hospitals, and pharmacies throughout Puerto Rico. Maintaining the quality and stability of pharmaceutical products is essential to ensure their effectiveness in prescribed treatments. One critical specification in this process is keeping the cold chain, which requires a constant temperature between 2°C and eight °C from preparation to delivery to the customer. This requirement is necessary to preserve the stability of the product and guarantee the effectiveness of the medicine, ensuring patient safety, minimizing financial losses, and establishing documentary evidence that provides a high level of security during the distribution process. The center serves distant areas such as Aguada, Sabana Grande, and Ricon, and failure to comply with these specifications can put the integrity of the pharmaceutical product at risk.

RESEARCH DESCRIPTION

The cold chain process for refrigerated products becomes crucially important, as its objective is to bring health to the patient through the delivery of reliable, effective, and high-quality pharmaceutical products. We face the challenge of using large, specific storage refrigerators that meet rigorous specifications to keep the product refrigerated within a temperature range of 2°c to 8°C during customer delivery.

We will conduct the cold chain qualification to address this specific need, focusing on the furthest delivery routes. It will be assessed using data loggers strategically placed to ensure no temperature changes over time during the delivery routes, thus ensuring the stability and quality of the medication.

RESEARCH OBJECTIVES

Evaluate and determine the pharmaceutical product distribution route system within the distribution center in Caguas to ensure compliance with the specified temperature range of 2°C to 8°C for the refrigeration of the farthest routes (Aguada, Abana Grander, and Rincon).

RESEARCH CONTRIBUTIONS

The qualification involves maintaining a constant cold temperature on the most distant routes, such as Aguada, Sabana Grande, and Ricon, throughout the distribution of pharmaceutical products. The refrigeration specifications range between 2°C and 8°C for delivery to various pharmacies in Puerto Rico. The main objective is to

use a DMAIC tool that helps us ensure that deliveries consistently meet the established parameters, maintaining the required temperature range from when the large Totes are sealed in the distribution center until they reach the customer.

LITERATURE REVIEW

A cold chain consists of a set of norms and procedures to ensure product handling, conservation, storage, and distribution within specific temperature ranges, guaranteeing their quality from the manufacturers' departure to the patient's arrival [1].

- Refrigerated: 2°C to 8°C
- Ambient Temperature: 15°C to 30°
- Controlled Room Temperature:20°C to 25°C
- Frozen Storage: -25°C to -10°C
- Cryogenic Freezing: -70°C to -180°C

The main processes within a cold chain are:

Reception: It involves receiving, inspecting, and delivering products to cold rooms.

Refrigerated Storage: It involves keeping products in refrigerated facilities or devices that maintain a constant temperature within the desired range specification.

Handling: During the handling of refrigerated products, it is essential to follow proper practices to minimize exposure to unwanted temperatures.

Refrigerated Transport: This involves transporting temperature-sensitive products in refrigerated vehicles or with suitable cooling systems to maintain a constant temperature throughout the journey.

Temperature Monitoring: Continuous temperature monitoring is essential during all cold chain processes from storage to final delivery. This is achieved using temperature monitoring devices that record and alert any deviations outside the established range.

Pharmaceutical Product Logistics

The logistics of pharmaceutical products present distinctive particularities compared to other sectors, as ensuring product quality involves compliance with good manufacturing, storage, distribution, and transportation practices and meeting the requirements established by regulatory agencies.

Guidelines and technical guides issued by the World Health Organization (WHO) and the United States Pharmacopeia (USP) are followed to comply with good manufacturing practices. The United States of Pharmacopeia (USP) established in its report 40- chapter 1079 the following as “Good Storage and Distribution Practices for Medicines”: “Pharmaceutical manufacturers must consider the primary, secondary, and tertiary packaging that best protects the drug during its storage and distribution.” “The packaging (tertiary or subsequent) for drug distribution must be selected and checked to ensure the maintenance of product quality to protect the contents from the rigors of distribution, including environmental or physical damage. “The packaging used to transport the drug must be qualified based on the state condition, as well as temperatures sensitive to ensure the quality and safety of the products” [2] [3].

DMAIC

It is a methodology that helps solve identified problems in an organization [4] [5]. The name is an acronym and indicates the five stages of the method.

- **Define (D):** Identify the problem and analyze the organization's situation and the context in which it operates.
- **Measure (M):** Taking measurements within the process to analyze situations.
- **Analyze (A):** With the collected data, it is possible to determine and analyze why the process is failing, how a short-term solution could be implemented, and assign responsibilities to it.
- **Improve (I):** This stage indicates the actions necessary to improve the process, i.e., an improvement plan. To do this, you can use improvement tools, and the essential risk must also be measured to implement the improvement.

- **Control (C):** After the improvement has been made, measurements should continue to ensure that the improvement has permanently helped solve the problem. If other issues are detected, it should return to the initial definition phase for continuous and progressive improvement.

METHODOLOGY

The execution of the Cold Chain Qualification in the logistics of pharmaceutical products was carried out using the DMAIC methodology. This methodology is part of the Six Sigma tools that contribute to the best performance and success of the projects. The abbreviation of DMAIC reflects the five fundamental phases of the methodology: define, measure, analyze, improve, and control.

Define Phase

During the first phase, the project charter is developed, detailing the objectives, scopes, challenges, timeline, stakeholders, and critical aspects that will facilitate monitoring and control of the improvement process. This step is vital, as it officially validates the project and clarifies the metrics to be improved. During this project stage, the project objectives are identified, ensuring proper handling and distribution of pharmaceutical products that require storage between 2°C and 8°C. A clear definition of the project is established with the team, ensuring that each strategy and objective is aligned with the company's expectations.

Measure Phase

In the measurement phases, the impact of the refrigerated product distribution system on the farthest routes, such as Aguada, Sabana Grande, and Ricon, will be evaluated concerning customer delivery, aiming to determine if it stays within the specified temperature range of 2°C to 8°C throughout the distribution process.

Table 1
Distance of the Routes

Caguas to the Destination		
Routes	Approximate Distance	Approximate Time
Sabana Grande	81 miles	2 hours
Rincon	102 miles	3 hours
Aguada	115 miles	3.5 hours

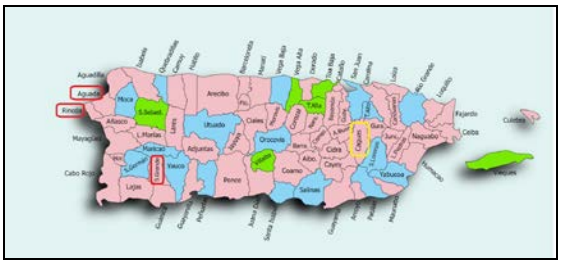

Figure 1
Map of Puerto Rico with the Farthest Routes

Analyze Phase

During the analysis phase, the Ishikawa diagram, also known as the cause-and-effect diagram or fishbone diagram, was employed to break down the potential causes of the identified problem. This diagram allowed for the systematic organization of different categories of influences that could affect the maintenance of the specified temperature range of 2°C to 8°C on the furthest distribution routes of refrigerated products, such as Aguada, Sabana Grande, and Ricon. By breaking down these categories into specific sub-causes, such as the distribution process, refrigeration equipment, weather conditions, and product handling, we were able to identify a wide range of possible contributing factors to the problem.

The detailed analysis provided us with a deeper understanding of critical areas requiring attention and helped us prioritize our actions to effectively address the challenge of maintaining the appropriate temperature throughout the distribution process.

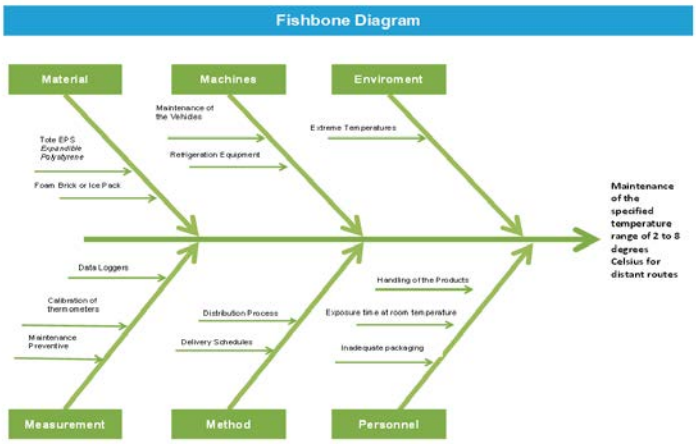

Figure 2
Fishbone Diagram

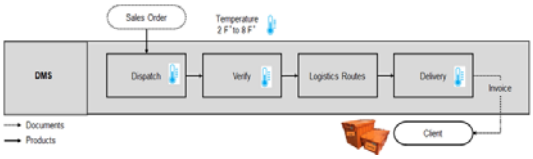

Figure 3
Distribution Process

Improve Phase

During the Improvement phase, effective solutions will be implemented to address the root causes identified during the analysis, with an emphasis on validating and always maintaining the appropriate temperature. Temperature monitoring test will be carried out on the most distant routes to verify time and temperatures, ensuring compliance with the 2°C to 8°C specifications.

Control Phase

In the Control phase, measures and protocols will be established to monitor compliance with temperature standards closely, thus ensuring the integrity of the cold chain throughout the logistics process.

RESULTS AND DISCUSSION

This section presents the analysis of results and discussion of the problem established and how it was achieved to ensure that deliveries consistently meet the established parameters, maintaining the required temperature range from the moment the large totes are sealed until they reach clients, using DMAIC methodology for this project.

Define

In this section, a chapter of the project was developed to detail the status of the objectives, scope, challenges, schedule, interested parties, and key aspects that facilitate the monitoring and control of the project improvement process. This ensures that each strategy and objective is aligned with the company's expectations and meets regulatory requirements, thus ensuring product quality and stability. Refer to Figure 4 Project Chapter.

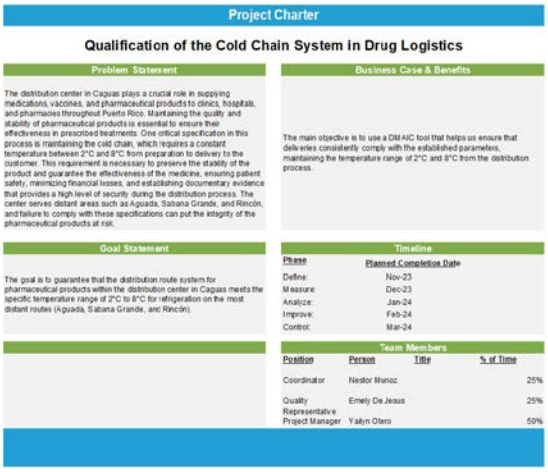

Figure 4
Project Charter

Measure

During the measurement phase, a list of shipping routes for the distribution of products was evaluated, analyzing the different routes to identify which were the furthest from delivery to customer. In addition, the procedures that support the merchandise loading process were evaluated for the shipment of products to customers.

Table 2
List of the Routes

Number Route	Routes	Approximate Time	Number Route	Routes	Approximate Time
1	Aguada-Rincón	2.5 hours	31	Morovis	1 hour
2	Moca- Añasco	2 hours	32	Corozal	50 minutes
3	Mayagüez A	1.55 hours	33	Barranquitas A1	1 hours
4	Mayagüez B		34	Naranjito-Toa Alta	51 minutes
5	San Sebastián	1.50 hours	35	Toa Alta-Toa Baja	51 minutes
6	San Sebastián-Moca	1.57 hours	36	Dorado-Toa Baja	40 minutes
7	Moca	2.03 hours	37	Toa Baja 1	40 minutes
8	Aguadilla A	2.01 hours	38	Carolina A2	40 minutes
9	Aguadilla B	2.01 hours	39	Bayamón-Catano	28 minutes
10	Cabo Rojo-Hormigueros	1.54 hours	40	Bayamón B	32 minutes
11	Hormigueros-San German	1.45 hours	41	Bayamón A	32 minutes
12	Guánica-Lajas	1.29 hours	42	Guaynabo-Bayamón	25 minutes
13	Adjuntas-Jayuya	1.25 hours	43	Área Metro C	30 minutes
14	Utuado-Lares A1		44	Área Metro A	30 minutes
15	Isabela	1.42 hours	45	Guaynabo- Puerto Nuevo	22 minutes
16	Lares	1.34 hours	46	Santurce	23 minutes
17	Camuy-Quebradillas	1.19 hours	47	Guaynabo A2	22 minutes
18	Hatillo	1.16 hours	48	Guaynabo Pueblo	22 minutes
19	San German-Sabana Grande	1.39 hours	49	Santurce	
20	Yauco-Guayanilla	1hr 22 min	50	Hato Rey-Rio Piedras	25 minutes
21	Ponce A1	1.05 hours	51	Hospital Metro	30 minutes
22	Ponce A2	1.05 hours	52	Truiillo Alto	28 minutes
23	Penuelas-Guayanilla	1.19 hours	53	Caguas	15 minutes
24	Arecibo-Hatillo	1.17 hours	54	Carolina-A	40 minutes
25	Arecibo	1.20 hours	55	Carolina-B	40 minutes
26	Florida-Barceloneta	1.10 hours	56	Carolina-C	40 minutes
27	Manati-Vega Baja	48 minutes	57	Guayama	49 minutes
28	Manati- Vega Baja A	59 minutes	58	Villalba-Juana Diaz	1.08 hours
29	Vega Alta-Vega Baja	43 minutes	59	Coamo-Santa Isabel	59 minutes
30	Orocovis-Morovis C	1.21 hours	60	Juana Diaz-Villalba	58 minutes

Analyze

During the analysis phase of the DMAIC cycle, the Ishikawa diagram, also known as the cause-and-effect or fishbone diagram, was developed to break down the possible causes of the identified problem in Figure 2 Ishikawa Diagram. This diagram allowed for the systematic organization of different categories of influences that could affect the maintenance of the specified temperature range of 2 to 8 degrees Celsius in the distribution routes farthest from refrigerated products, such as Aguada, Sabana Grande, and Rincón, which were measured in the measurement phase. By subdividing these categories into specific sub-causes, such as the distribution process, refrigeration equipment, weather conditions, product handling, and vehicle maintenance, we were able to identify a wide range of potential contributing factors to the problem.

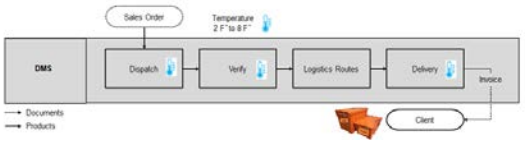

Figure 5
Distribution Process

Distribution Process

Order Dispatch, Verification and Shipping:

- Order Dispatch and Verification process: are defined, and procedures are in place to guarantee that each order is dispatched and verified by means of labels, NDC, item number, lot or batch number, and quantity.
- A second operator (different from who dispatches the order) verifies all orders prior to shipment to assure the accuracy of the order with the documentation. Invoices are required to identify the selected lots, batch numbers, expiration dates of the products, and quantities. Shipping processing procedures are defined to ensure all orders are verified before shipment, and documentation complies with applicable laws and regulations.
- Packaging: The products destined for various pharmacies are dispatched the following day. At the beginning of the workday, the shipping operator verifies that the orders to be prepared are refrigerated and the quantity to be sent per customer and route.
- At the Distribution Center, logistics and transportation are coordinated to meet all customer requirements through designated delivery routes and times. Customer orders cut is scheduled at the following specific times: 11:00 am, 12:00 pm, 1:00 pm, 2:00 pm, 3:00 pm, 6:00 pm, and 7:00 pm, ensuring that

customers receive their orders. The months of October, November and December 2023 were evaluated to validate compliance with delivery schedules.

Table 3
Dashboard On-time Delivery Routes

ON TIME DELIVERY

AM 91%					PM 99%				
MONTH	AM				MONTH	PM			
	<10:00am	<11:00am	>11:00am			<06:00pm	<07:00pm	>07:00pm
October	91%	3%	6%		October	99%	1%	0%
November	91%	7%	2%		November	99%	1%	0%
December	91%	9%	0%		December	99%	1%	0%

Refrigeration Equipment

- Expandable Polystyrene (EPS): The English acronym for "Expandable Polystryrene" translated into Spanish as "Poliestireno Expandido", refers to a foamed plastic material derived from polystyrene and shaped into packaging. It allows for storing materials at high/low temperatures, thereby maintaining a temperature range for a specified period.

Figure 6
Expandable Polystyrene

- Foam Brick: Design that provides reliable protection and maintains temperature for a wide variety of products and/or packages. It has a block of frozen foam, and its packaging is similar to that of an ice pack. According to the qualification, these require meeting a precondition of 72 hours of freezing in temperatures between -25°C and – 15°C (-13°F and 5°F) before being used.

Figure 7
Foam Brick FPP64

- Shipping system that maintains the temperature required by Manufacturers to transit refrigerated merchandise (36-46°F/ 2-8°C). This consists of a plastic bag assembled with an EPS container and configured with the corresponding quantity/size of foam bricks.

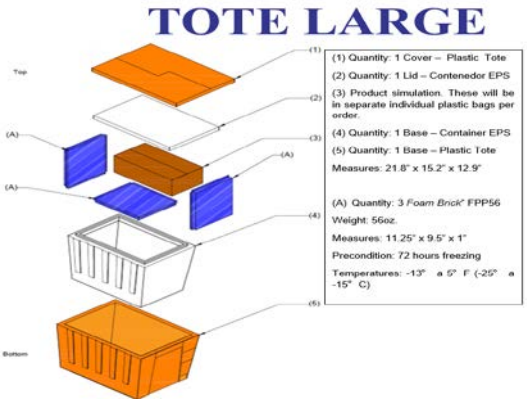

Figure 8
Totes for Shipping

The refrigerated product shipping system is carried out as follows.

Figure 9
Shipping System Configuration

Weather Conditions

During the evaluation phase in January 2024, the AccuWeather tool was used to obtain detailed measurements of temperatures in both the Caguas area and more distant delivery routes, such as Sabana Grande, Rincon, and Aguada. This approach provided us with precise information on the behavior of ambient temperatures during the evaluation period [6].

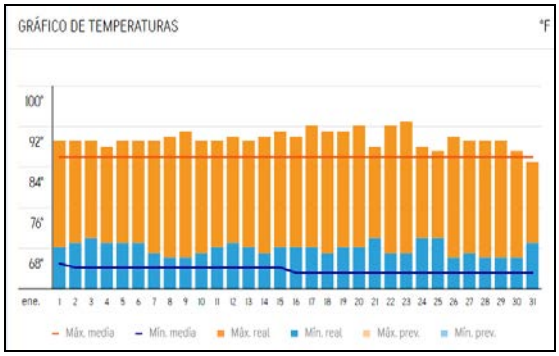

Figure 10
Weather Temperature Caguas

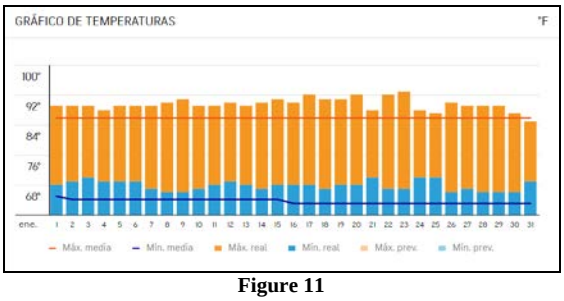

Figure 11

Weather Temperature Rincon

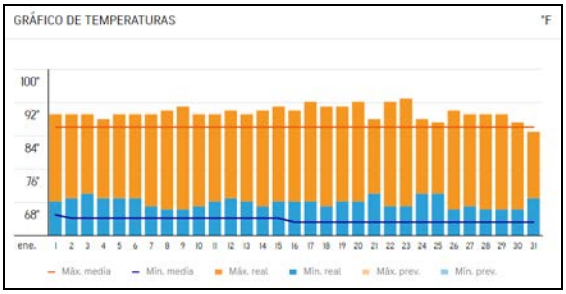

Figure 12

Weather Temperature Sabana Grande

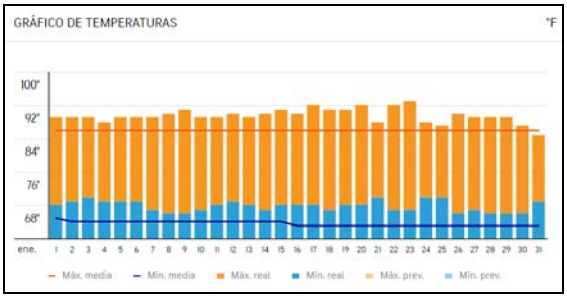

Figure 13

Weather Temperature Aguada

Product Handling

An evaluation of the shipping system configuration was carried out to ensure that it will be carried out according to the required specifications, to ensure maintenance of the temperature between 2°C to 8°C.

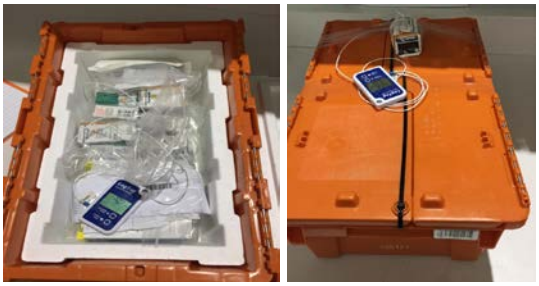

Figure 14

System Large Tote Configuration

Improve

During the Improvement stage, the calibrated TRED30-16R or TRED30-7R data logger, a temperature measurement device designed specifically for refrigerated products, was incorporated into the shipping System configuration process. This instrument provides detailed data that allows temperature monitoring detection of deviations, and corrective action to ensure that products remain within the required range and meet quality standards. Its ability to continuously record temperature readings over time makes it an invaluable tool for enhancing refrigeration system performance and refining the logistics process.

Figure 15

TRED30-16R Log Tag

The analysis carried out, for three days, a sampling of the most distant routes, such as Sabana Grande, Rincon, and Aguada, to verify the shipping period and verify that the product is maintained between 2 and 8 degrees Celsius during delivery to the various customers of these routes. The tests were carried out on January 3,4 and 5, 2024.

Based on the execution of the test, the results were as follows:

Table 4

Sabana Grande Route Test Data

Route 019 San German-Sabana Grande			Acceptance Criteria: 2 °C to 8°C Reading- Every 5 minutes		
Date	Log Tag Identification	Departure time from Caguas	Time of arrival to a client	Temperature °C	Pass or fail
01-03-2024	LT-020 TRE30-7R Serial Number # 1360008564	5:00 am	7:23 am	2.8	Pass
01-04-2024	LT-019 TR-30-7R Serial Number # 1360008628	4:45 am	7:27 am	3.9	Pass
01-05-2024	LT-016 TRE30-16R Serial Number # A06100238730	4:40 am	7:25 am	2.5	Pass

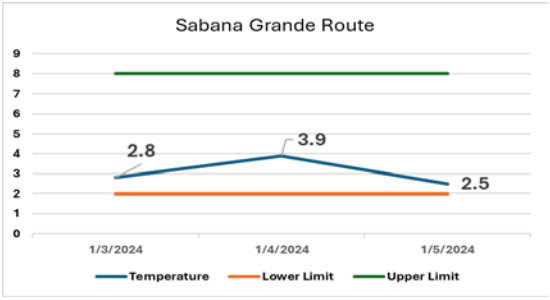

Figure 16
Chart of the Sampling for Three Days

Table 5
Ricon Route Test Data

Route Rincon			Acceptance Criteria: 2 °C to 8°C Reading- Every 5 minutes		
Date	Log Tag Identification	Departure time from Caguas	Time of arrival to a client	Temperature °C	Pass or fail
01-03-2024	LT-17 TRE30-16R Serial Number # AA061002388DH	5:00 am	9:06 am	2.0	Pass
01-04-2024	LT-021 TR-30-7R Serial Number # 1360008629	4:54 am	9:41 am	2.2	Pass
01-05-2024	LT-021 TR-30-7R Serial Number # 1360008629	5:15 am	9:17 am	2.3	Pass

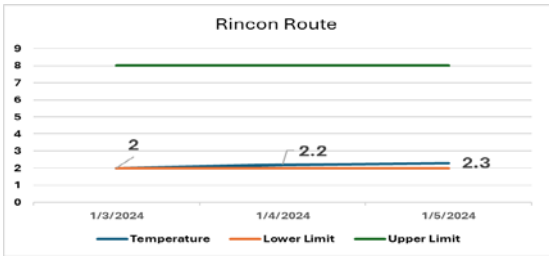

Figure 17
Chart of the Sampling for Three Days Ricon Route Test

Table 6
Aguada route Test Data

Route Aguada			Acceptance Criteria: 2 °C to 8°C Reading- Every 5 minutes		
Date	Log Tag Identification	Departure time from Caguas	Time of arrival to a client	Temperature °C	Pass or fail
01-03-2024	LT-17 TRE30-16R Serial Number # AA061002388DH	5:45 am	8:45 am	2.0	Pass
01-04-2024	LT-018 TR-30-16R Serial Number # A061002389NT	5:50 am	9:41 am	2.0	Pass
01-05-2024	LT-022 TR-30-7R Serial Number # 1360008563	6:00 am	9:00 am	2.1	Pass

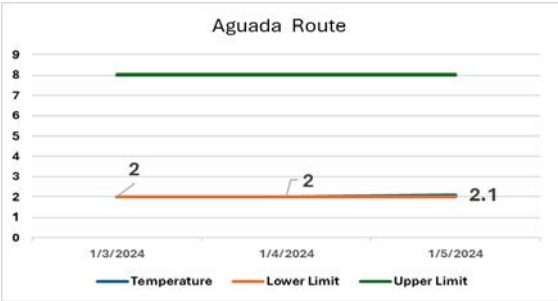

Figure 18
Chart of the Sampling for Three Days Aguada

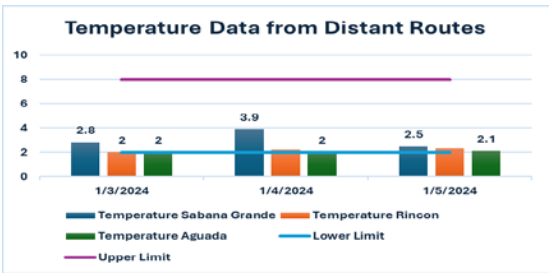

Figure 19
Temperature Data from Distant Routes

Control

During the Control phase of the DMAIC cycle, a validation protocol was developed to guarantee the quality, temperature, and safety of refrigerated products throughout the distribution chain to customers. This protocol includes clear guidelines on responsibilities, storage, transportation, and handling of products, as well as specific measures to monitor and record temperature conditions in real-time and address deviations that may arise. As part of the continuous improvement of the control phase, an annual verification of the protocol must be carried out to guarantee that the products are maintained at the temperature when distributed to customers.

Based on the creation of the protocol, the following sections were included:

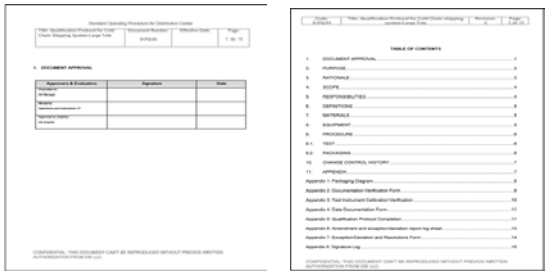

Figure 20
Qualification Protocol Documents

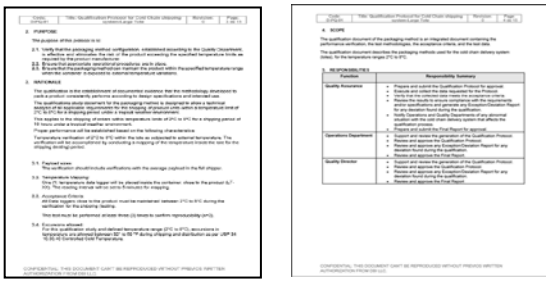

Figure 21
Qualification Protocol Documents

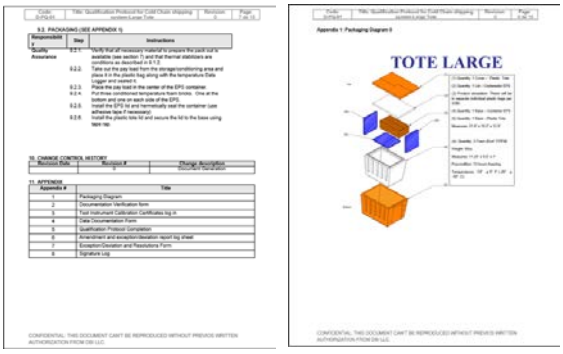

Figure 23
Qualification Protocol Documents

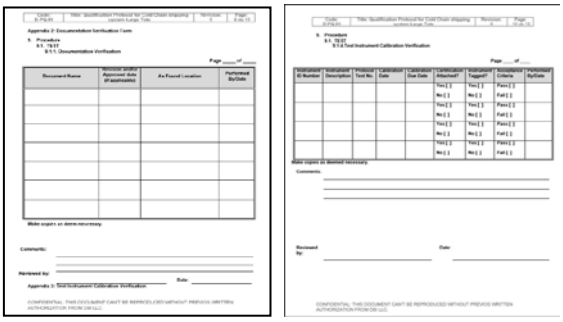

Figure 24
Qualification Protocol Documents

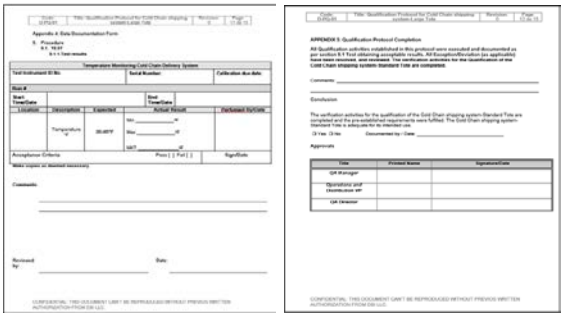

Figure 25
Qualification Protocol Documents

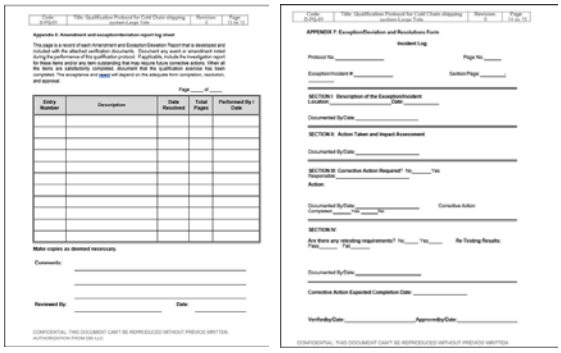

Figure 26
Qualification Protocol Documents

CONCLUSION

We can conclude that the Qualification of the Cold Chain System in Drug Logistics, using the DMAIC tool, has satisfactorily demonstrated compliance with the temperature parameters of 2°C to 8°C for refrigerated products. Through a rigorous planning, implementation, and monitoring process, it has been shown that products remain within the temperature ranges of 2°C to 8°C, even on the most distant routes such as Aguada, Sabana Grande, and Ricon. This shows that, regardless of the distance of the routes, the product maintains its temperature throughout the distribution chain until it reaches the customer.

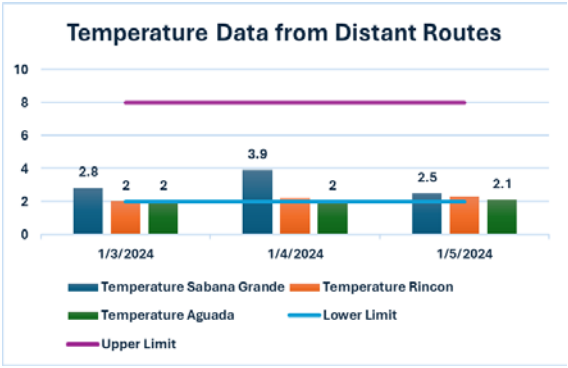

Figure 27
Temperature Data from Distant Routes

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