AdeptGroup

ENGINEERING EXCELLENCE

Managing Cold Chain

A PROCEDURE TO ESTABLISH A ROBUST COLD CHAIN STRATEGY

Cold Chain Case Examples

CASE 1 (FOOD INDUSTRY):
A meal-delivery company received multiple complaints from its customers regarding an unpleasant odor coming from the received packages. The root cause was identified to be an interrupted cold chain.

CASE 2 (PHARMACEUTICALS):
A pharmaceutical company sought out the feasibility of a direct-to-patient delivery model, which would allow for drugs to be delivered and administered at the patient's residence. Current regulations and GDP policies presented a variety of challenges to the company. More importantly, a minor temperature excursion or/and delay in delivery could have potentially compromised the life of the patient.

Cold chain refers to the storage and transport of temperature-sensitive products within the optimally required temperature from the manufacturing site until they reach the end-users. Pharmaceutical companies are dealing with an increasing growth in the need for temperature assured supply chains for their temperature-sensitive products. A consistent storage and shipment process is essential to ensure the product's integrity is sustained throughout the distribution environment.

In addition, regulatory compliance enforcement is becoming more stringent, to the extent that authorities require evidence that temperature-sensitive products have not only been stored at the temperature range provided on the label, but also kept within an approved temperature range during transportation and handling. Even a minor temperature excursion of temperature-sensitive products could lead to deterioration of the drug or loss of potency which could potentially jeopardize the patient's safety.

A recent literature-review study claimed that the percentage of vaccine exposure to temperatures out of recommended ranges during transport was 33% in wealthier countries and 37.1% in lower-income countries [1]. Another literature-review study [2] concluded that the exposure of vaccines to freezing temperatures in both developed and developing countries within storage and transport segments of the cold chain is pervasive. This signifies current and continuing issues facing the transport of temperature-sensitive products during various segments of the cold chain.

This white paper addresses the topics below pertaining to cold chain to effectively reduce the likelihood of temperature excursion outside of recommended ranges:

I. SOLUTION SELECTION CRITERIA FOR COLD CHAIN

II. STRATEGY FOR THERMAL QUALIFICATION

Temperature Excursion:
A temperature excursion is any temperature outside the recommended temperature range for a temperature-sensitive product.

I. Solution Selection Criteria for Cold Chain

One essential element of a smarter temperature-controlled supply chain is solution selection.

In principal, temperature-controlled shippers have a broad range of options. In order to select or develop a solution, these key elements, at minimum, should be considered:

TRANSIT TIME

How much time will it take for the product to reach its destination (including the time that the product will remain on the shipping dock at shipper's location and at the users' location)?

ANTICIPATED AMBIENT TEMPERATURE

The ambient conditions in which the shipper will be stored and transported should be considered.

REQUIRED TEMPERATURE RANGE (FROZEN, CRT, 2-8°C) AND ALLOWABLE TEMPERATURE EXCURSION

An acceptable temperature range should be determined based on the stability study results of the product being transported. Stability testing takes place outside the qualification process, and its purpose is to provide tangible evidence on how the quality of an active pharmaceutical ingredient varies with time under the influence of a variety of environmental factors such as temperature, light and humidity. The data produced from the stability testing determines the temperature and humidity the product can withstand and still maintain its potency and integrity.

COMPONENT STORAGE REQUIREMENT (E.G. CONDITIONING CONSIDERATIONS)

The process of exposing materials such as PCM plates, payload and insulator components to predetermined environmental (temperature/humidity) conditions for specific lengths of time in order to render the material fit for use should be taken into account.

I. Solution Selection Criteria for Cold Chain

TYPE OF SOLUTION (ACTIVE OR PASSIVE)

There are two basic categories for temperature-sensitive packaging: Passive and Active solutions.

Active systems use mechanical and/or electric systems powered by an energy source, combined with thermostatic control to control and maintain proper product temperatures. Passive systems commonly use phase change materials (PCM) such as water-based refrigerant, dry ice, liquid nitrogen, etc.

When making the choice between active and passive systems, the value of the product and the supply chain route will influence the decision, along with the required thermal protection and product volumes.

DISTRIBUTION ROUTE

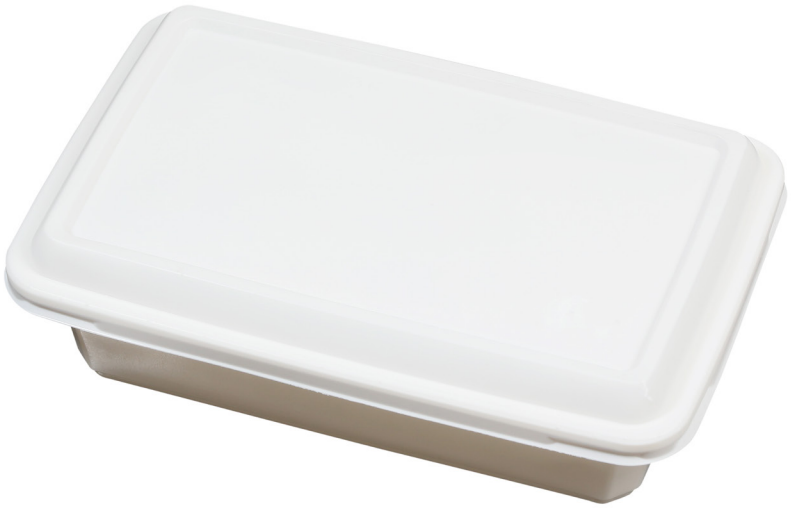
Transport routes from a point of origin to a destination should be considered and every Critical Control Point (CCP) should be identified. For instance, unloading a truck and placing on tarmac or entering a temperature-controlled warehouse.

APPLICABLE REGULATORY BODY

All national and international regulations with regard to safety, security, health and environment (e.g. dangerous goods, controlled substance, child resistance) must be considered during the selection life cycle of packaging configurations and cold chain solutions.

FDA 483 Citations related to cold chain:

Cite ID	Description
9097	Failure to maintain temperatures during shipment of Fresh Frozen Plasma at -18 °C or colder
4342	Drug products are not stored under conditions of [temperature] [humidity] [light] so that their identity, strength, quality and purity are not affected.



Identify Potential Risks

II. Strategy for Thermal Qualification

After a decision is made to further explore a cold chain system, a comprehensive strategy for qualification of the system needs to be initiated.

Prior to the qualification phase, potential risks should be identified, and related mitigation measures should be determined. The potential risks shall be revisited as needed after subsequent qualification phases to propose actions to remedy the major identified risks. The risk assessment helps ensure that the proposed qualification procedure matches the intended use.

In addition, User Requirement Specification (URS) lists the attributes, which are verifiable and unambiguous, assigned by the user prior to a qualification test to establish performance limits, should be documented. The URS document should be written from the user's viewpoint without defining the solution and should be structured to allow traceability through design and testing phases.

There are commonly four stages in the qualification process of thermal shippers: preparation/pre-qualification, Design Qualification, Operational Qualification and Performance Qualification.

PRE-QUALIFICATION

- Initiate strategy for qualification of the system
- Identify potential risks and determine related risk mitigation measures
- Document User Requirement Specification

DESIGN QUALIFICATION

- Detailed specifications & drawings of thermal shipping system
- Test procedure
- Define environmental temperature profiles
- Define total duration of test
- Representative payload configuration for the shipping system

OPERATIONAL QUALIFICATION

- Full details of packaging assembly, components and materials
- Defined temperature profile
- Load configurations
- Thermal mapping strategy
- Number of tests
- Seasonal testing
- Handling practices
- Equipment calibration
- Determined pre-approved acceptance criteria

PERFORMANCE QUALIFICATION

- Full details of packaging assembly, components and materials
- Transport modes and routes
- Load configurations
- Number of tests
- Placement of electronic data logging monitors
- Handling practices
- Determined pre-approved acceptance criteria

II. Strategy for Thermal Qualification

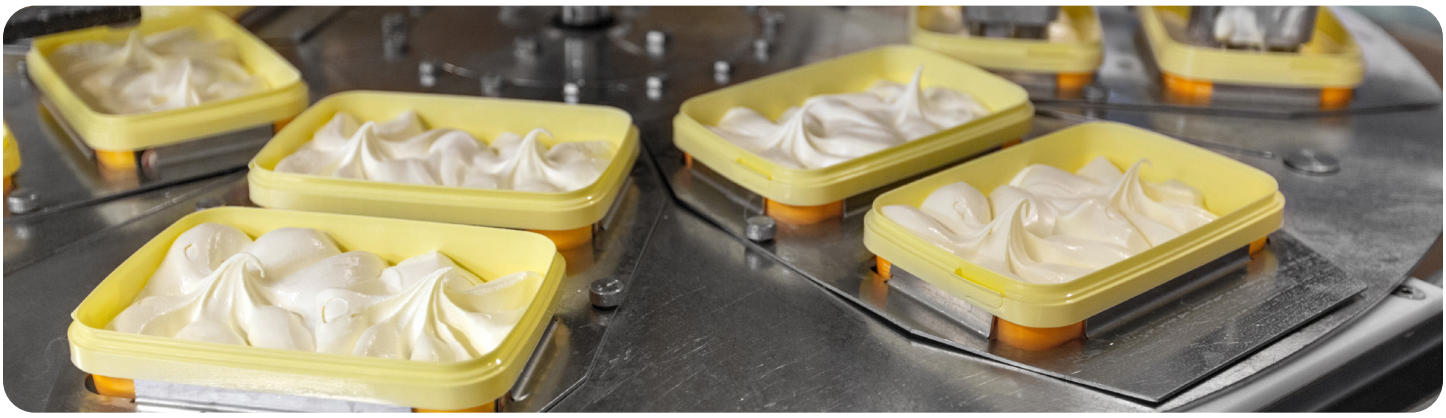
DESIGN QUALIFICATION (DQ)

The Design Qualification stage is completed to ensure that the thermal packaging system is capable of operating within established parameters indicative of real world performance. DQ generally enables the project team to initiate the qualification phase and verify the design. The DQ should generally address the specifications and drawings of the thermal system and test procedure, including defining the environmental temperature profiles, the total duration of the test and representative payload configuration for the shipping system.

OPERATIONAL QUALIFICATION (OQ)

After the DQ step, Operational Qualification is executed under laboratory-controlled, usually extreme, conditions. The OQ should be detailed in a well-defined protocol that lists the following at minimum:

- Full details of packaging assembly, components, and materials
- Defined temperature profile
- Load configurations (maximum and minimum loads)
- Placement of Electronic Data Logging Monitors (thermal mapping strategy)
- Number of tests
- Seasonal testing
- Handling practices
- Equipment calibration
- Determining pre-approved acceptance criteria



II. Strategy for Thermal Qualification

It is also important during the OQ step to define temperature profiles. There are three approaches for defining temperature profiles:

1. **Standard temperature profiles** – The usage of standard temperature profiles (e.g. ISTA 7E and 7D) from third-party institutions are usually warranted if no data is available for an associated distribution lane. As these temperature profiles represent extreme cases, testing the qualified shipper against these standard profiles might cause it to be deemed over-engineered for actual shipments. However, ISTA's standard indicates that cycle profiles are general simulations not intended to represent a worst case temperature exposure.
2. **Existing shipment data** – This approach involves monitoring the actual temperature that the shippers experience during the supply chain over a specific period of time. Although this approach takes a significant amount of time and resources, it is the most accurate results.
3. **Theoretical-based temperature profile models** – In this model, the rationale is determined based on geographical weather data or other relevant information about the distribution environment. In general, profiles may differ as a result of geography, transportation supply lanes, handling practices, modes of transport or transit time.

PERFORMANCE QUALIFICATION

The final phase of qualification is Performance Qualification. Performance Qualification would involve a field shipment in the real operating environment. The protocol for Performance Qualification must include:

- Full details of a packaging assembly, materials and components
- Transport modes and routes (overnight air, international, ground, etc.)
- Load configurations (maximum and minimum loads)
- Number of tests
- Handling practices
- Placement of Electronic Data Logging Monitors
  - Payload monitor(s)
  - Ambient monitor(s)
- Equipment Calibration
- Determined pre-approved acceptance criteria

II. Strategy for Thermal Qualification

Both thermal and physical performance should be assessed, and the results should be documented in a formal final report.

In addition to the thermal qualification of thermal shippers, mechanical qualification, including stress and vibration testing, is essential to evaluate the robustness of the package throughout the distribution chain. The stresses of shock and vibration during shipment can potentially compromise the thermal system by displacing or puncturing the insulation system, inducing leakage in the phase change material containers, compromising container closure integrity (CCI) of payload, etc.

There are testing standards (ASTM D4169, ASTM D7386, ISTA 3A) that can be used to simulate the stresses that a shipper can experience during transport. Companies that do not test properly can find their temperature-controlled shippers showing suboptimal performance in actual shipment.

Get in Touch

Partner Selection for Process Development

In order to devise an impeccable cold chain solution, many independent factors should be considered and assessed.

The proposed solutions should be systematically validated in accordance to design requirements and regulatory mandates. The complete process development requires extensive expertise, time, and organization.

Manufacturers often seek packaging engineering services suppliers with experience in temperature-controlled packaging to assist them with process development and qualification activities. This approach allows for a swift and cost-efficient fix without burdening the internal team.

Companies like Adept Group can help clients develop a standardized, repeatable process to establish a proper solution for cold chain. Adept Group has the capability and experience to assist clients with the establishment of packaging configuration and thermal shipping systems qualification life cycle:

With over twenty years of experience, over seventy packaging engineers and multiple packaging engineering teams, Adept Group has the depth and breadth to manage client needs that may arise throughout any aspect of the cold chain.

adeptpackaging.com

References

1. C. M. Hanson et al., “Is freezing in the vaccine cold chain an ongoing issue? A literature review”, Vaccine, Volume 35, Pages 2127-2133.
2. D. M. Matthias et al., “Freezing temperatures in the vaccine cold chain: A systematic literature review”, Vaccine, Volume 25, Pages 3980-3986.