

Good Cold Chain Management Practices for Controlled Room Temperature Shipments

The pharmaceutical industry, currently under increasing global regulatory scrutiny, is expanding Good Cold Chain Management Practices (GCCMP) for standard Cold Chain Products (2°C to 8°C) to include the storage and transport of “Ambient”/Controlled Room Temperature (CRT) products. The industry is moving toward an expanded inclusion that will help to ensure product quality and patient safety.

After a thorough review of the current regulatory developments and key challenges, this article will provide advice and methodology regarding how to best approach CRT shipments. The recommendations are based on two main concepts: Risk Assessment and Continuous Improvement.

Regulatory Environment

Some countries, such as Saudi Arabia, Ireland and Argentina, have existing regulations in place requiring control of CRT shipments. Globally, the latest changes in regulations have given rise to increased discussion around concepts like maintaining storage label claims during distribution, the use of stability data, Risk Assessment and the need for documentation supporting Continuous Improvement across the distribution environment.

The Parenteral Drug Association (PDA) was one of the first to include CRT products in its guidelines. The PDA's 2007 revised Technical Report 39 states that “these products may be shipped outside of their respective label storage conditions provided stability data or scientific/technical justifications exist demonstrating that product quality is not affected and meets the national and international requirements.” The United States Pharmacopeia (USP) adopted a similar approach: “Drug products can be transported, at temperatures outside of their labeled storage temperatures if stability data and relevant scientific justification demonstrate that product quality is maintained.”¹

The recently published European Good Distribution Practices guidelines dictate that “the required storage conditions for medicinal products should be maintained during transportation within the defined limits as described by the manufacturers or on the outer packaging”² and that “appropriate corrective and preventive actions be taken to not only correct deviations but also prevent them.”³ This standard practice is in line with the principles of quality risk management.

Options and Corresponding Challenges

As a result, three options are available:

- Ship purely according to label claims.
- Ship based on stability data (i.e., purposefully ship outside label claim).
- Use a scientific and risk-based approach (i.e., define an approach to effectively manage exceptions).

Ship purely according to label claims

European regulators favor the option of shipping purely according to label claims. Conditions on the label have been set to allow the medicinal product to maintain its quality until the expiry date. Relying on stability data to justify excursions that will not impact overall product quality, including carrying the product out to the expiration date, adds additional complexity. Furthermore, the manufacturer is often the only actor in the distribution chain who has access to such data. Transparency is needed to support the scientific justification for such excursions. Yet, transparency is not easily achieved, documented, or managed.

Shipping CRT products, much like cold chain products, is not always straightforward or cost-effective. Maintaining the USP-defined temperature range for CRT products is often deemed more technologically challenging. The industry has also adopted different ranges to allow for some flexibility. When considering passive solutions, more protective packaging material will be needed, leading to higher volume/weight and higher shipping costs for what are on average much lower retail-valued products.

Ship based on stability data

This option offers the most flexibility, but data would have to be shared if it is available at all. CRT shipments historically have not been monitored by manufacturers or their supply chain partners, so often representatives of the pharmaceutical supply chain will lack data to support uncontrolled conditions beyond label claim. Without such data, an organization cannot be sure that the solutions used for transport actually maintain and guarantee product integrity. Should some temperature data be present, will it be enough to evaluate the impact of excursions on the product? Some products might be shipped through new lanes with new environmental conditions, which might not have been taken into account in the stability studies.

Use a scientific and risk-based approach

Finally, using the principles of Risk Assessment, one could choose to ship according to label claims with known data and build the case for allowable pre-defined exceptions based on scientific rationale. This position is the one adopted by the European Federation of Pharmaceutical Industries and Associations (EFPIA).

While this model largely provides the most cost-effective and flexible program for managing CRT shipments, a number of steps are required to provide appropriate documentation to support such a model. This need for clear documentation includes ongoing monitoring to prove that the conditions for the allowed excursions are respected, and the development of appropriate Standard Operating Procedures (SOPs) along the supply chain.

Goal

The goal is to define a cost-effective approach for controlled ambient logistics while ensuring patient safety, product quality and regulatory compliance. This includes defining product requirements, conducting shipping route analyses and developing a decision-making methodology that defines controlled ambient shipping and monitoring requirements.

Dataloggers can be a resourceful tool for controlled ambient shipments. Initially, dataloggers should be used to analyze temperatures along a given route. There are several factors to consider for both analysis and sensor selection including: (1) product value and stability, (2) shipping lane, (3) mode and service-level of transportation, and (4) seasonality.

Product Value and Stability

The organization should apply a risk assessment based on, but not limited to, the criticality of the ailment being treated by the product (i.e., if the product is adulterated what is the potential that a patient will experience a negative impact?), the value per shipment, product availability, manufacturing constraints, and the impact to the company if an excursion is experienced. Along with product value, an analysis of product stability should also be completed.

Many products have stability data, but many transportation lanes will experience the effects of seasonality and will exceed the available stability without adequate protection and appropriately defined operating procedures. However, not all ambient temperatures will exceed the stability requirements, thus necessitating a cost-effective approach for selecting the proper protection to maintain product temperature. The organization should develop a plan to test products, expand their stability, and understand at what level their products fail due to extreme temperatures. Conducting these studies at specific soaking temperatures that exceed the planned temperatures such as 30°C, 40°C (or higher) depending on the expected ambient extremes is suggested. Examples of detailed stability protocols can be found in PDA Technical Report 53 “Guidance for Industry: Stability Testing to Support Distribution of New Drug Products.”

The stability budget (time and temperature) for each product should be allocated to the full lifecycle: manufacturing, storage, and distribution process. Fixed amounts of the budget are allocated to those areas that are most in control, such as manufacturing and storage. Once the proper amount of time and temperature budget is assigned to manufacturing and storage, the remaining budget can be allocated where it is most needed, to distribution, the most variable portion of the product lifecycle.

Defining stability at 40°C, 50°C, 60°C, etc., and testing to failure, along with conducting cycling tests that closely resemble real-world temperature fluctuations, will enable the organization to better understand the limitations of the products and compare those limitations to lane-specific temperature data. The comparison of stability to lane temperature data will enable the organization to develop a more cost-effective solution.

Shipping Study

The first step to analyzing a shipping lane is to thermally map the equipment that will be used during transportation. Thermal mapping is the process of placing sensors in a grid pattern throughout the space. Thermal mappings can be completed on trailers, trucks, lorries, air containers, sea containers, pallet shippers, small parcels, etc. Analyzing the data collected from the thermal mapping will enable one to understand how the route, time of year, and other factors, such as load pattern, affect temperature throughout the space.

This understanding of the data enables one to determine those locations in the space that have the greatest heat, cold, and variability. These locations are defined as the worst-case locations and are used to define a monitor placement protocol used for ongoing monitoring programs. This is a critical first step so that collecting data during the next step in the Shipping Study will ensure that the data corresponds to the worst-case scenario. USP <1079> “Good Storage and Shipping Practices” recommends conducting three separate thermal mappings along a route to define the worst case scenarios. Once the thermal mapping is complete and monitoring location(s) have been defined, the next step is to gather temperature data along multiple shipping lanes. The shipping lanes should be represented by origin and destination geographies. With the involvement of a Quality Department, it is possible to establish optimal targets to ensure a broad representation of the seasonal dynamics of each lane.

Most regulatory agencies require an analysis of peak hot and cold seasons. For most regions, studies are conducted in January and February, and then again in July and August. Weather websites can be used to determine peak times of the year. Temperature should be checked at the origin and destination, and along the route. Shipments going from the northern hemisphere to the southern hemisphere (and vice versa) typically see the most extreme change in temperatures.

Data from enough shipments should be collected to be considered statistically reliable. While the International Safe Transit Association (ISTA) recommends a sample size of 25 shipments per variable such as: origin, destination, carrier, and mode of transportation, statisticians typically require a minimum of 30 samples to attain minimum reliability. According to the central limit theorem, conducting fewer than 30 samples has a much lower reliability because it could miss an extreme event. The ultimate goal of the shipping study is to develop an analysis of the thermal variability a typical product or shipment may experience and to quantify and predict risk. There are two types of analysis: Ambient Temperature Profile and Time Above and Below Thresholds (TABT).

The goal in developing an ATP is to document the ambient conditions so that appropriate thermal protection can be defined. There are different methodologies available to develop an ATP. This is typically done by measuring and recording the distribution of ambient temperatures over time and then analyzing the information to produce a model used to predict extremes. Actual shipments are consequently matched against the model to test its accuracy. Historical standard models (such as the one from ISTA) essentially average temperature records to create a single profile. However, using Sensitech’s newly developed Risk Controlled Ambient Thermal Profile (RCATP) methodology provides a means of quantifying the risk of temperature excursions on both the upper and lower limits. In addition, this methodology uniquely allows for modifications to the created profile based on risk tolerance.

TABT is a useful analysis that defines the amount of time that a shipment or route will spend above or below specific defined temperature thresholds. The thresholds typically match to the same thresholds that are defined in the stability testing. For example, if for the stability testing, thresholds of 25°C, 30°C, 40°C, and 50°C are selected; the same thresholds should be established and used to analyze the temperature data collected for each shipment and route. Using the same threshold will allow for comparisons between the stability data and the temperature data collected along the routes.

Comparing Stability to the Shipping Study for the Production of Decision Tools

After completing the first two primary tasks: defining and improving stability knowledge for the products in question, and understanding the ambient temperature expectations for specific routes, the next step is to compare the stability data to the shipping study TABT. Comparing the product's stability against the TABT associated with the applicable routes will result in groupings of products and routes. These groups will include products that have similar stability requirements. Some of the product groups will be more sensitive to temperature. Routes will also be grouped based on severity, some routes will be more moderate and others more extreme during specific times of the year.

The outcome of the comparison will be a matrix, one side a list of products and the other side a list of routes. The matrix will define where additional protection (specialty packaging or logistics services) is required for each product, along each route, during specific times of the year. The completed matrix (see Figure 1) will serve as a decision support tool to assist an organization's logistics department in planning transportation needs.

FIGURE 1

Decision Support Matrix

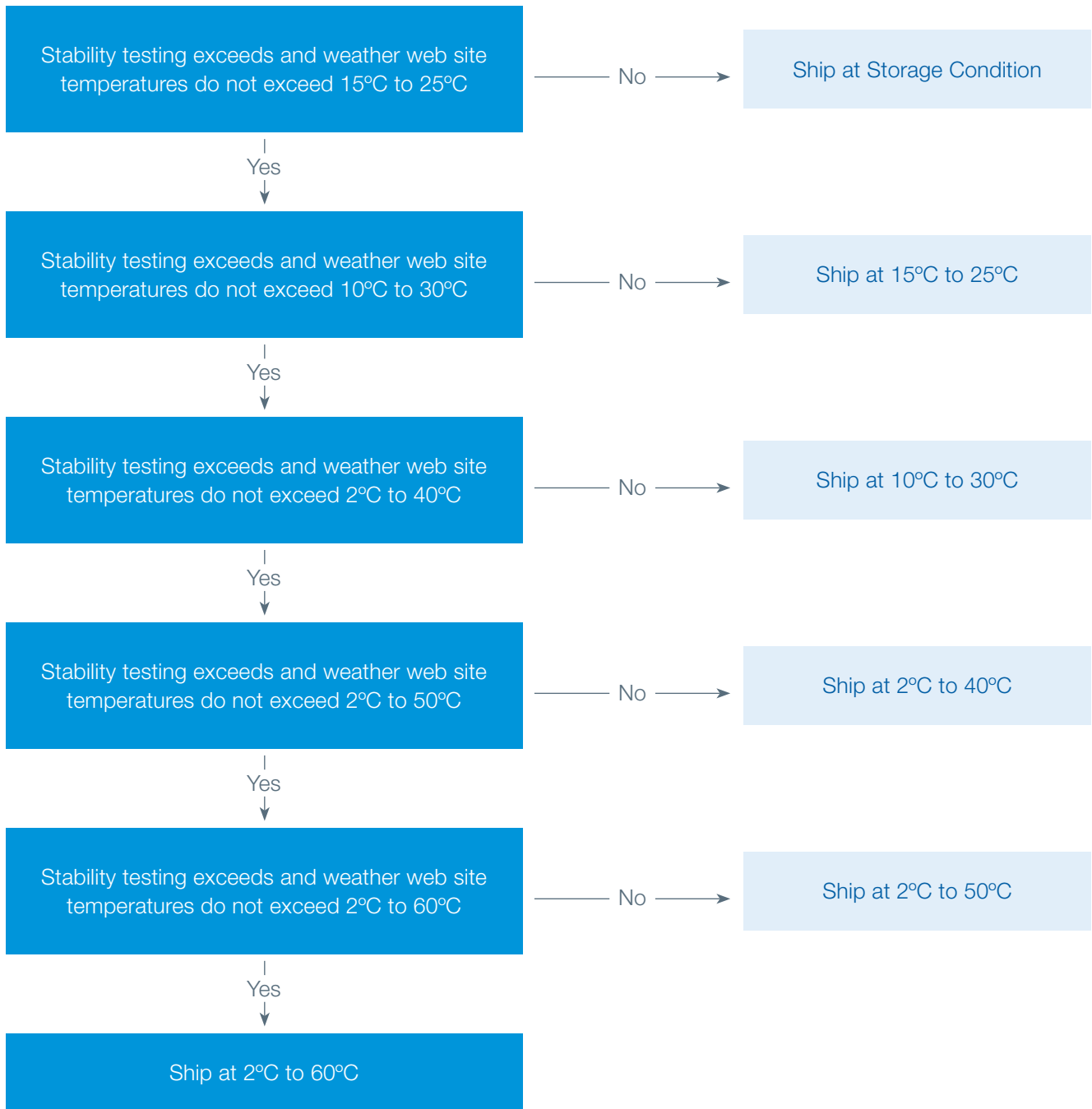
Route	PRODUCT											
	Low Stability Product				Moderate Stability Product				High Stability Product			
	Product 1	Product 2	Product 3	Product 4	Product 5	Product 6	Product 7	Product 8	Product 9	Product 10	Product 11	Product 12
Zone 1 to Zone 1	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Zone 1 to Zone 2	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Zone 1 to Zone 3	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Zone 1 to Zone 4	Red	Red	Red	Red	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow
Zone 2 to Zone 1	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Zone 2 to Zone 2	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Zone 2 to Zone 3	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Zone 2 to Zone 4	Red	Red	Red	Red	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow
Zone 3 to Zone 1	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Zone 3 to Zone 2	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Zone 3 to Zone 3	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Zone 3 to Zone 4	Red	Red	Red	Red	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow
Zone 4 to Zone 1	Red	Red	Red	Red	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow
Zone 4 to Zone 2	Red	Red	Red	Red	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow
Zone 4 to Zone 3	Red	Red	Red	Red	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow
Zone 4 to Zone 4	Red	Red	Red	Red	Orange	Orange	Orange	Orange	Yellow	Yellow	Yellow	Yellow

- Lower risk for this product on this route, check specific daily temperatures to see if adverse temperatures are expected
- Moderate risk for this product on this route, check specific daily temperatures to see if adverse temperatures are expected
- High risk for this product on this route, check specific daily temperatures to see if adverse temperatures are expected

Depending on the amount of thermal variability along a given route, a decision tree may be helpful in managing overall protective supply chain needs. The goal of a decision tree is to develop a process that allows the organization to make cost-effective decisions on distribution and monitoring requirements. The tree is based on the product-route matrix and defines the solutions including: carrier, temperature control requirements, service-level, and monitoring requirements. The decision tree (see Figure 2) can be enhanced with weather information to make a predictive model.

FIGURE 2

Ambient Shipment Decision Tree



Correlating the data gathered from the Shipping Study with data gathered from weather reports enables the organization to develop a predictive model decision tree. The decision tree allows the organization to see what temperatures are predicted along a given route, and predict through the model what to expect for product temperatures. From this predicted product temperature, the correct thermal protection can be selected.

Conclusion

The steps required to cost-effectively manage the distribution of CRT products include:

- Evaluation of stability data
- Expansion of stability data
- Thermal mapping studies
- Shipping lane studies
- Ambient temperature analyses
- Time above and below analyses
- Product route matrix
- Decision tree defining protection and monitoring requirements

Understanding the requirements of specific products and expanding the stability range for each product may be more cost-effective than temperature-controlled logistics. Grouping products by similar stability requirements and comparing them to the ambient temperature analysis from a Shipping Study enables an organization to implement a risk-based approach to define the most effective protective logistics and monitoring schemes possible.

- i USP <1079> “Good Storage and Distribution Practices for Drug Products,” August, 2014.
- ii European Commission “Guidelines on Good Distribution Practice of Medicinal Products for Human Use,” November, 2013.
- iii Ibid.