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Liquid Cryogenic Storage Chamber Qualification

By John Orange Feb 27, 2019 6:10 am PST

ABSTRACT

Cold chain storage of biopharmaceutical products and associated materials is required to maintain product stability and is a regulatory expectation. Critical areas of concern in cold chain practice related to liquid nitrogen cryogenic storage include container selection, method of temperature monitoring, and qualification approach based on risk management. Qualification of liquid nitrogen cryogenic storage equipment is described in a three-step process:

1. Understanding cryogenic storage chambers
2. Using your cryogenic storage chamber
3. Qualifying your cryogenic storage chamber.

INTRODUCTION

Cold chain storage of biopharmaceutical products and associated materials is a vital concern in regulated industries. Temperature control of cold chain storage throughout the entire cold chain process is required to maintain product stability. Cold chain storage practices have come under scrutiny from auditors and regulatory agency inspectors in recent years. Chamber qualification for temperature controlled equipment intended for storage or for vessels intended to be used during shipping is now a regulatory expectation.

Cold chain storage begins at the source of manufacturing where products or materials are kept cool or frozen until delivery to their final destination for administration to the patient. References to cold chain storage range from refrigerated conditions to cryogenic conditions. While refrigerated (2-8°C) transport conditions are always a concern, significant attention is also being paid to cryogenic conditions (-196°C), specifically liquid nitrogen vapor-phase material storage. Critical areas of concern in cold chain practice related to cryogenic storage chambers include transportation, method of temperature monitoring during transport, and qualification approach for permanent storage solutions.

Cryogenic Transportation

Companies involved in cold chain storage under cryogenic conditions must be attentive to a number of factors from how material is packed to the method of transportation used for transport. Finding the correct vessel or container and appropriate packing materials to control temperature for an extended period of time can prove challenging. The International Safe Transit Association (ISTA) provides guidelines identifying test scenarios for packaging. Many companies are embracing the recommendations of the ISTA and are identifying more robust safeguards for their cold chain shipping by vetting their processes and performing rigorous testing on their packaging and shipping practices.

Temperature Monitoring During Transport

The monitoring of products and materials during transport is also a critical piece of the cold chain process. Traditionally, a temperature recording datalogger is placed with the shipment and data is downloaded upon arrival at its final destination. This is a reactive approach that leaves the end user questioning whether or not their product remained within specifications during transport. Advances in technology are allowing product owners to be proactive with the use of live data-monitoring sensors. Monitoring sensors connect to cellular networks to transmit data to product owners to track the environmental conditions and locations during real time through the entire shipping route. If the conditions deviate from the specification range, the problem can be addressed during transportation by reacting to potential temperature threats long before the product arrives at the final destination.

In addition to ground transportation, air transportation is being impacted with respect to identifying or reinforcing cold chain storage strategies as well. Storage locations in airports for cold chain storage are held to standards defined by the International Air Transit Association (IATA). The IATA has developed a Center for Excellence of Independent Validators which is initiating a global standard for air shipment compliance in pharmaceutical storage practices.

Until recently, the focus on biopharmaceutical storage and transport has been limited to pharmaceutical companies. As cold chain best practices evolve, the focus has grown to include transportation and distribution strategies across the globe.

While maintaining temperature control during transport is a vital part of the cold chain, it is just as important to consider permanent storage before and after transport.

Controlled temperature unit qualification is a key part of demonstrating compliance in cGMP regulated cold chain applications. Since the operation of a permanent cryogenic storage chamber differs from that of a typical controlled temperature unit, such as a refrigerator, this white paper was created to help identify typical operation and standardized qualification of cryogenic storage chambers in accordance with validation best practices.

The following information applies to cryogenic storage chambers installed in a permanent or semi-permanent location.

Qualification of Cryogenic Storage Equipment

The qualification of liquid nitrogen cryogenic storage equipment may be considered to be a three-step process as follows:

1. Understanding cryogenic storage chambers
2. Using Your Cryogenic Storage Chamber
3. Qualifying Your Cryogenic Storage Chamber.

1. UNDERSTANDING CRYOGENIC STORAGE CHAMBERS

Understanding how your particular cryogenic or Liquid Nitrogen (LN2) chamber works along with some general facts will help determine how to qualify your LN2 chamber. Cryogenic storage chambers are used to store material in a suspended or inactive state. Cell banks, cell tissues, and other types of human or animal samples are commonly stored in these types of chambers. For example, cell banks are stored in these cryogenic conditions long-term until needed for manufacturing. An approach to mitigating complete loss is to store this type of material at two separate sites to support a robust disaster recovery strategy.

LN2 Liquid Level Control

In general, LN2 chambers for cryogenic storage are liquid-level controlled – they are not temperature controlled. The LN2 operation is controlled by at least two liquid level settings, either by using pressure sensors or thermistors to determine liquid level measurement. For reference purposes, the liquid level settings will be designated “High Level LN2” and “Low Level LN2” settings. When the “Low Level LN2” setting is triggered, the controller will call for a LN2 fill, a process where LN2 fills the bottom of the chamber until the “High Level LN2” setting is triggered. Temperature stratification will be widest before a LN2 fill begins and narrowest after a LN2 fill is completed. This process will repeat indefinitely during normal operation. The duration of time between LN2 fills is dependent upon the size of the chamber, load conditions, environmental/ambient conditions, and the distance between the active High and Low Level LN2 settings. This duration of time is considered a full cycle.

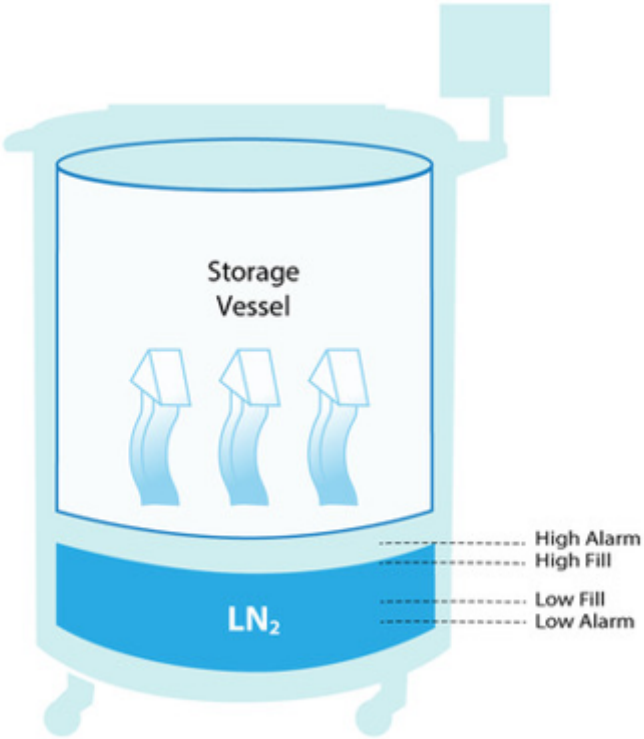

Figure 1. Cryogenic Storage Vessel

Temperature Zones Within the Chamber

Liquid nitrogen is contained at the bottom of the chamber and temperatures within the chamber are colder near the LN2 and are warmer away from the liquid. With that information, you can assume that temperature zones within the unit are planar and exhibit stratification, trending colder at the bottom and warmer (worst case) at the top of the unit.

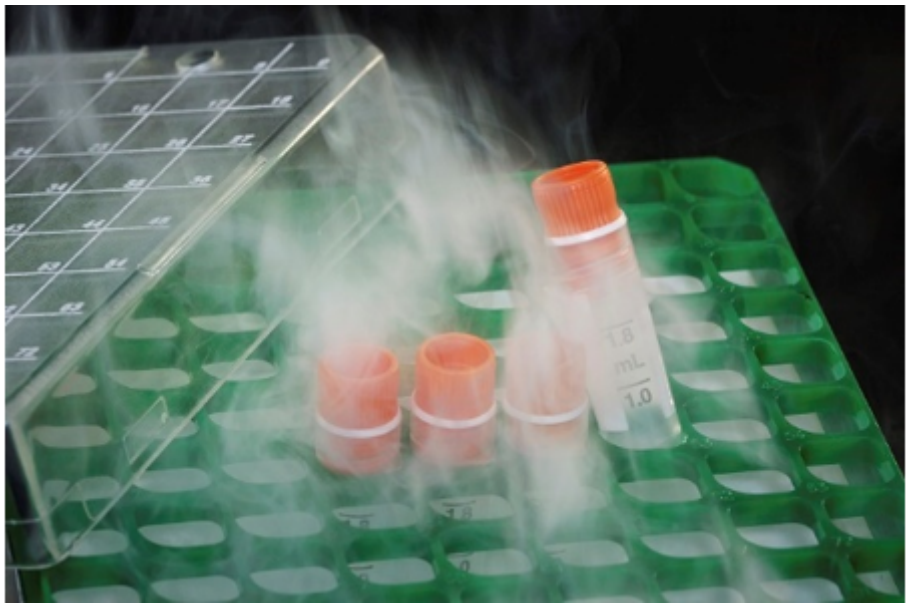

Figure 2. Materials for Cryogenic Storage

2. USING YOUR CRYOGENIC STORAGE CHAMBER

Determining how you intend to use your chamber will provide you with the blueprint to move forward into qualification. This should be a combination of considerations between both the use of the chamber and the product requirements.

LN2 Liquid Level Determination

Prior to qualification, the product SME / organization should determine if product should be stored in liquid phase or vapor phase within the LN2 chamber. The Liquid Nitrogen phase changes at approximately -195.79°C at atmospheric pressure. This is the expected product temperature if product is stored in liquid phase. The liquid level settings can be modified to fit storage requirements to target liquid or vapor phase storage. The larger the gap between fill/stop reduces the amount of internal storage space as liquid level will increase. The settings can also be modified to increase or decrease the LN2 fill frequency - LN2 fill duration increases as distance between the active liquid level settings increase. The same is true for the amount of LN2 in the chamber. Generally, larger units can contain more LN2 and as such, will take more time to evaporate as opposed to a smaller unit

Identify Your Temperature Range

LN2 chambers can come equipped with alarm functionality that will trigger when the controller/display RTD reaches a high temperature set point. It is important to know what the high temperature set point is of your unit (e.g. -135°C). This set point is determined by the technical function and is directly correlated to product storage conditions of the intended contents. This temperature will also ultimately define the temperature acceptance criteria for validation.

Safety Considerations

Adequate Personal Protective Equipment (PPE) must be worn when working with LN2. These include cryogenic-rated gloves, safety glasses, face shield, apron, and related equipment as applicable. Oxygen monitors are typically installed in rooms with LN2 chambers because oxygen is displaced by nitrogen gas and can cause asphyxiation. Doors to these rooms are left open when occupied placing the vent away from operators.

Figure 3. Personal Protective Equipment

3. QUALIFYING YOUR CRYOGENIC STORAGE CHAMBER

Qualification of the LN2 chamber can be performed once the initial setup parameters have been identified and implemented. The acceptance criteria for temperature distribution should be based on product storage conditions of tended contents identified by the technical experts.

Study Types and Test Durations

Once acceptance criteria are established, the study types and test durations can be determined. It is recommended that at least one full cycle of temperature data are recorded (e.g., 3 days); however, three full cycles would demonstrate more data points and complies with a best practice approach. Contrary to typical controlled temperature unit validation, capturing data for a set period of time (e.g., 24 hours) will likely only reveal data from a segment of a full cycle and is not suggested as a best practice as it may not capture worst case data just prior to the next fill cycle. Technical experts can determine if the qualification should capture temperature mapping under empty chamber and/or loaded chamber conditions and whether an open door study should be performed. A LN2 failure study can also be conducted to determine how long the chamber stays within range after a LN2 fill triggers and does not receive LN2. This test is usually performed to demonstrate temperature conformity in the event of LN2 shortage or an extended-time power loss.

Test Equipment Considerations

It is recommended that a 22AWG thermocouple be used for testing due to the extreme cold temperatures as the thin gauge thermocouples (e.g. 28AWG) are more susceptible to damage in LN2 conditions. Temperature sensors should be placed inside the chamber and divided among at least three different planes of temperature: bottom, middle, and top. It is important not to place temperature sensors above the storage containing area inside the vessel as this space is part of a thermal barrier and ultimately not a part of the storage envelope within the unit - temperature data from this area will not be representative of intended product storage. It is ideal to also place a sensor near the controller / display RTD of the unit and the monitoring RTD within the unit if available. The study should begin by triggering a manual LN2 fill in order to bracket full cycles more clearly.

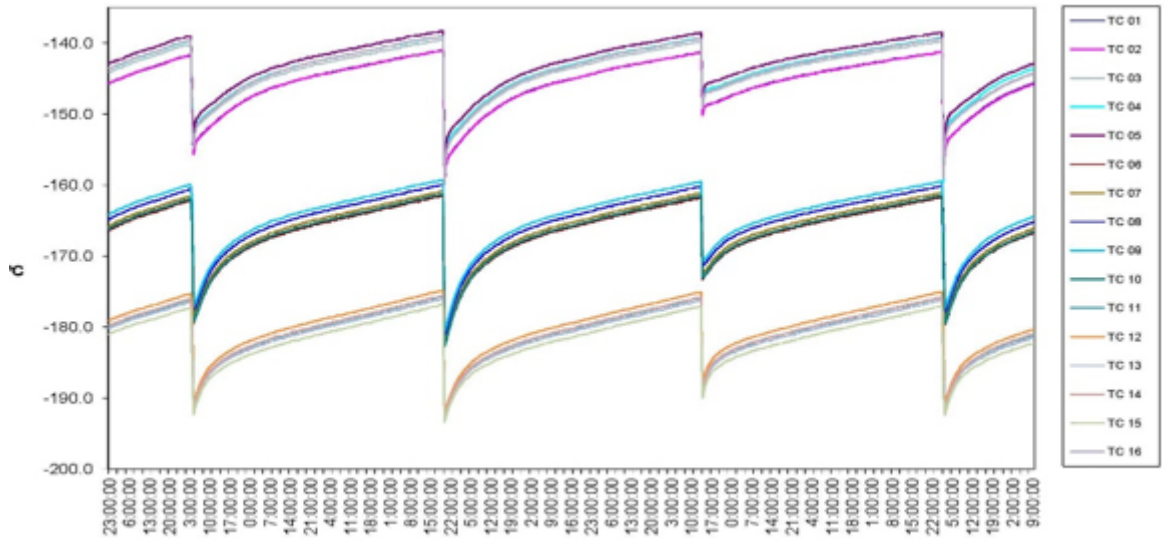

Figure 4. This graph demonstrates planar temperature zones within the unit and shows stratification, trending colder at the bottom and warmer at the top of the unit. This graph also reveals at least three full cycles which complies with a best practice approach.

SUMMARY

Cold chain storage of biopharmaceutic products and associated materials is a vital concern in regulated industries. Temperature control of cold chain storage throughout the entire cold chain process is required to maintain product stability and is a regulatory expectation. Regulatory auditors routinely inquire about cryogenic storage conditions and compliance to identified process controls. This discussion has addressed critical areas of concern related to cold chain practices with an emphasis on liquid nitrogen cryogenic storage. This includes transportation, method of temperature monitoring during transport, and qualification approach for permanent storage solutions. Identifying the correct vessel or container and associated packing materials to control temperature for an extended period of time is vital. Proactive temperature monitoring in real time is highly recommended.

A three-step LN2 qualification process is described:

1. Understanding cryogenic storage chambers. This involves how your particular cryogenic chamber works. LN2 chambers for cryogenic storage are generally liquid-level controlled.
2. Using your cryogenic storage chamber. Determining how you intend to use your chamber will provide you with the blueprint to move forward into qualification. Product storage in the liquid phase or vapor phase is determined. Qualification temperature range is then determined. Adequate ventilation with oxygen monitoring is mandatory and Personal Protective Equipment (PPE) must be worn when working with LN2.
3. Qualifying your cryogenic storage chamber. Once acceptance criteria are established, the study types and test durations can be determined. At least one full cycle of temperature data must be recorded;

three full cycles would demonstrate more data points and complies with a best practice approach. Temperature mapping under empty chamber and/or loaded chamber conditions and whether an open door study may also be performed in validation.

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