LN_2 Cryogenic Storage Chamber Qualification in 3 Steps

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3 Key Steps in Cryogenic Storage Chamber Qualification

Fig. 1: Controlled temperature unit qualification is a key part of demonstrating compliance in cGMP regulated applications. Since the operation of a cryogenic storage chamber differs from that of a typical controlled temperature unit, this white paper was created to help identify typical operation and standardized qualification of cryogenic storage chambers in accordance with validation best practices.

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. The following information on understanding your LN2 chamber may help guide you into making that determination.

LN2 Liquid Levels

In general, LN2 chambers are not temperature controlled - they are liquid-level 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 of this paper, the liquid level settings will be referred to as the "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 completes. 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.

Temperature Zones within the Chamber

LN2 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.

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.

Determining the Liquid Level of your Chamber

Prior to qualification, the end user should determine if product should be stored in liquid phase or vapor phase within the LN2 chamber. Liquid Nitrogen phase changes at approximately -195.79°C at atmospheric pressure which is the temperature that one can expect their product to be if stored in liquid phase. The liquid level settings can be modified to fit the requirements of the end user in order 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. Likewise for the amount of LN2 in the chamber. Generally, larger units can contain more LN2and as such, will take more time to evaporate as opposed to a smaller unit - this will also factor into a full cycle duration.

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).

Typically, this set point is determined by the end user and is directly correlated to product storage conditions of the intended contents and will ultimately define the temperature acceptance criteria for validation.

Safety Considerations

Adequate Personal Protective Equipment should be worn when working with LN2, such as cryogenic rated gloves, safety glasses, face shield, apron, etc. when applicable. Oxygen Monitors are typically installed in rooms with LN2 chambers because oxygen is displaced by nitrogen gas and can cause asphyxiation. Generally, doors to these rooms are left open when occupied placing the vent away from operators.

3: Qualifying your Cryogenic Storage Chamber

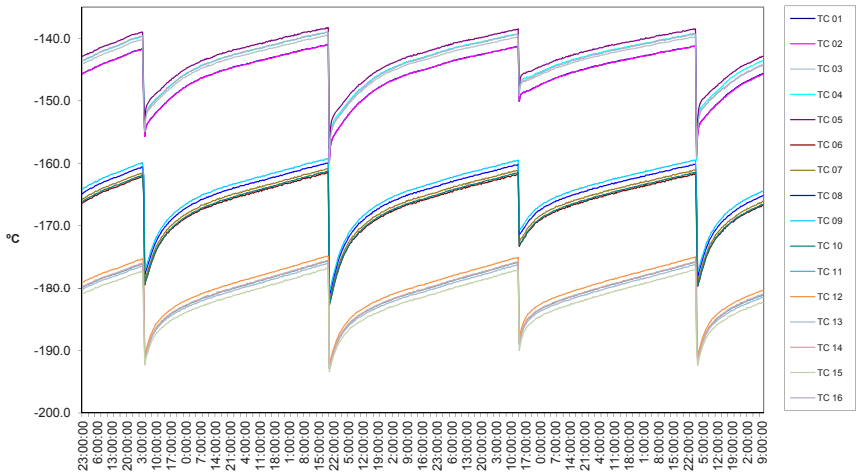

Fig. 2: This graph demonstrates planar temperature zones within the unit and shows stratification, trending colder at the bottom and warmer at the top of the unit. This graph also reveals at least three full cycles which complies with a best practice approach.

Note: An industry best practice would suggest placement of an external monitoring sensor placed in the warmest location identified in the qualification.

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 the intended contents identified by the end user.

Study Types & Test Durations

Once the acceptance criteria is established, the study types & test durations can be determined. It is recommended that at least one full cycle of temperature data is captured (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. The end user can determine if the qualification should capture temperature mapping under empty chamber and/or loaded chamber conditions and whether or not 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 if the end user intends to demonstrate temperature conformity in the event of LN2 shortage or an extended power loss scenario.

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's important not to place temperature sensors above the storage containing area inside of 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.

Ideally, the study should begin by triggering a manual LN2 fill in order to bracket full cycles more clearly. Record data until the desired amount of full cycles are captured.

Masy BioServices can qualify your LN2 chambers with unparalleled accuracy and precision. Ensure your cryogenic storage chambers are performing to your specifications. Contact Masy today to learn about our qualification and validation services.

Learn more at www.masy.com

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