Process Considerations for Cryogenic Shipping

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LN2 is used to deliver life-saving cell and gene therapies. Kite’s autologous supply chain (meaning we use an individual patient’s cells to manufacture a therapy for that specific patient) relies heavily on the ability to ship our final product efficiently and without issue. We use dry vapor LN2 shippers to transport our final product, and I’ll be summarizing what we’ve found to be best practices for shipping cryogenically.
Setting up a cryogenic cold chain is no trivial task
May be very different from a typical supply chain
Couriers are not used to having this much responsibility
The stakes are high

Failure could lead to adverse patient impact or complete loss of product
The first consideration when shipping using LN2 is safety for everyone involved.

Of course, proper PPE must be worn whenever you are dealing with LN2. At -196°C, this stuff will burn you immediately. Filling, or “charging”, the shipper with LN2 requires pouring LN2 into the dewar using a hose. As splashing could occur, gloves, a face shield, and an apron are a must.

Dry vapor shippers are typically used because of the safety advantages they offer over shipping with liquid nitrogen. Liquid nitrogen can slosh around and spill if tipped over, but dry vapor shippers contain an absorbent medium to keep the liquid nitrogen in place around the edges of the container, and the product in the middle is kept cold only by the vapor that emanates from the absorbed liquid.

As part of the charging process, excess liquid nitrogen must be poured out of the shipper. The shippers we use weight about 70 pounds, so they are not easy to lift and tilt. Our partner, Cryoport, who we lease our LN2 shippers from, is developing a fixture to facilitate the pour out process using a simple lever.
LN2 temperatures also make it very difficult for labels to adhere with sufficient strength.

It can be helpful to partner with labeling companies that have expertise in their materials to suggest the right adhesive for your specific application.

Once a few material options have been selected, a full material qualification is necessary to ensure the label remains adhered through worst-case simulated processing (extreme temperatures and durations for storage, shipping, etc.).

After a single material is chosen, it is important to standardize the application process (using any tools needed) to ensure that, for example, a pressure sensitive label has sufficient and even pressure applied during application.
The extreme cold of liquid nitrogen vapor also reduces the strength of most materials.

When selecting materials for the primary container, among many other things, consider the glass transition temperature of the material. This is the temperature at which polymers become hard and brittle, like glass.

Once a material has been selected, testing must be performed to ensure the full packaging system is able to maintain the physical integrity of the primary package. Industry standard shock and vibration testing can be used to simulate actual distribution forces. Failure can be catastrophic if the correct controls are not put in place to reduce the forces experienced by the primary container in transit.

In order to help minimize the trauma the product experiences, it must be very clear to everyone involved that the package must be handled with care.
In order to provide confidence in the packaging and shipping process used to transport material cryogenically, it is important to perform thorough qualification of both the packaging system (through Operational Qualification) and the shipping process (through Performance Qualification).

Title 21 of the CFR provides requirements for the temperature of products during shipment, along with other general requirements for warehousing and distribution.

Several organizations maintain guidance documents for packaging design and testing, and product distribution. These documents can be used to supplement the CFR requirements, and design qualification testing that sufficiently provides evidence of the robustness of your packaging materials and shipping process. When designing your packaging and shipping qualification, it is important to consider:

- The locations and durations of your expected shipping lanes
  - How long does your packaging need to maintain temperature?
- The environmental conditions along your expected shipping lanes
  - What temperature does your packaging need to insulate against?
- The need for passive vs. active temperature control
  - Can a passive shipper maintain appropriate temperatures for the duration needed?
- The effects of your product load configuration on the performance of your packaging
  - Is a minimum thermal mass needed to stabilize internal temperatures during shipment?
- The physical trauma possible along your expected shipping lanes
  - Will you ship via road or air?
  - Are drop and vibration testing necessary?

Without robust qualification testing, regulatory bodies may not accept your packaging materials and/or shipping process as sufficient to maintain the safety and efficacy of your products. Some common issues with qualification testing as reported by the FDA are:

- Unacceptable explanations of temperature excursions during shipping
- Temperature probes in the incorrect location (not worst case)
- Qualified duration of shipper not correlated to actual shipping times
- Lack of seasonal variation in shipping studies
- Poor performance of budget packaging materials
Lastly, packaging providers, 3PLs, couriers, and everyone else involved in the shipping process needs to be fully invested in your success.

Start by building relationships with your partners. Visit their sites. Have them visit your site. Have lunch with them. Setup a QBR to meet regularly and discuss their performance. You need to know these people intimately, and they need to know your business intimately.

Train these people so that they understand how they are adding value. They are not just moving around toilet paper from amazon, they are part of a chain interconnected in a process to save someone’s life. They need to know that dropping your package could literally be the difference between life and death for someone.

And finally, a Quality Agreement is a must to ensure that expectations are clear up front. This is where you can capture special requirements like handling, temperature control, communication channels, and anything else you need your partners to do to ensure the safety, quality, and efficacy of your product.
Follow These Best Practices

- Safety: Put PPE and safety procedures in place
- Label Adhesion: Select and test appropriate adhesives
- Primary Container Integrity: Design to protect primary package
- Packaging and Shipping Qualification: Execute appropriate qualification tests
- Supply Chain Partners: Build relationships with your partners