WHITE PAPER

The Uninterrupted Cryogenic Supply Chain: Why Data is King

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The Uninterrupted Cryogenic Supply Chain: Why Data is King

The biologics supply chain is fraught with problems. These large molecule products and their earlier materials are more sensitive to environmental impact, and therefore require extreme careful handling during transportation. Here we will dig into each step in the cryogenic supply chain, and evaluate how your data monitoring practices can make all the difference ensuring a smooth, uninterrupted supply chain.

Biologics today

The nature of medicines development today is extraordinary. Regenerating cells with novel technology to heal organs in the body is fascinating and mind blowing only a couple decades ago. The opportunity to correct serious diseases using gene-editing technology, viral vectors and cell-based therapies is beyond exciting to patients and the healthcare community.

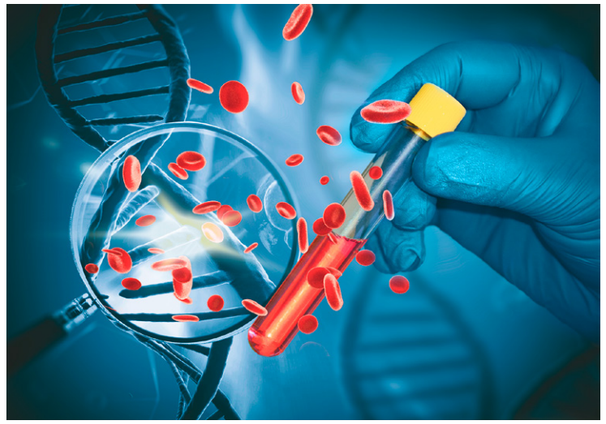
Governments around the world are striving to keep up with the pace of development, creating provisions for fast track approvals of some regenerative medicines, while at the same time ensuring ethical and patient safety using GxP guidance documents.

"Cellular and gene therapy-related research and development in the United States continues to grow at a fast rate, with a high number of products advancing in clinical development." US FDA

What impact do these innovative medicines and therapies have on supply chains? How can the distribution environments be controlled enough to ensure these life-saving therapies, and biologically based medicines are not ruined before reaching the patient? Is your clinical supply chain ready for handling more bio-based materials?

Let's explore this further and assess how biological samples, materials and cell-based therapies require extreme careful handling, at ultra-low or cryogenic temperatures.

We will look at 1) Critical data – that matters to you
2) Evaluate cryo shipping processes to ensure they are running as smooth as possible without interruptions.



Critical Parameters Data

Frozen is frozen, right? It used to be that sending a cryo shipment was straightforward – freeze it and its good to go. For some materials such as blood or bodily fluids, that still may be the case. However, we now know that more sensitive shipments, such as cell-based therapies, DNA and some human tissues, are affected by many factors including tilt orientation, shake, vibration and temperature. Not to mention the preservation methods used to freeze and thaw DNA is a critical process to ensure sample or product quality throughout distribution.

So how do you know what's right for your product? Product Development will carry out stability studies that will define the critical parameters your product, sample or IMP (Investigational Medical Product) that needs to be maintained throughout distribution.

Why are these critical parameters so important? Clearly, these parameters set the specifications for the quality and efficacy of your product or samples. Having data from reliable sensors will not only prove to you, and all your supply chains stakeholders the product is ok, but also to regulators. As the biotech industry increases submissions, global regulators will become more skilled in evaluating these specialized products and asking for the critical data to prove patient safety.

Preparing a Cryo Shipment

Consider: *A probe is a probe, right?*

There are different types of probes but Pt100 have become the industry standard because they ensure accuracy. Some monitoring solutions include other connectors as well, such as the M8 that provide an even more stable to ensure the data is transmitted securely.

Whichever monitoring you use, best practice is to conduct a full system qualification to ensure all the pieces of the monitoring system function properly in practice.

Consider: *Have you received a cryo shipment and the data logger is blank?*

A cryo shipment via air is exposed to external pressure at higher altitudes, which can lead to LN2 vapor leakage. This in turn could affect internal container temperature, but also could result in the monitoring device being damaged such as the circuit board or battery due to extreme cold conditions on the electronic device. With no monitor… there is no documentation. A bad situation indeed.

It's also worth checking with your provider to ensure the sealant and mounting processes could not be the cause.

Consider: *Are you able to use specific configuration settings on your logger that can save you time during your LN2 charging or filling processes?*

For example, is the data logger displaying temperature measurements while the tank is being charged or filled? Can you configure the logger so that the monitoring starts when the container reaches -196 °C saving you time so that you can add samples when conditions are optimal. Can you pause the alarm? 'Pausing' an alarm is documented on the PDF report, which saves you time and hassle of having to stop your logger, run and save PDF reports and re-start your logger. As the journey continues, PDF reports can be read out any time.

Cryo Shipping Challenges

Receiving a Cryo Shipment

Consider: *The shipment received has an alarm, but the report is not clear.*

There's temperature spike at the same time for several similar shipments. What's going on? It could be container opening when LN2 is being refilled or recharged? On further inspection, that is correct based on feedback from the courier. What should you do with this alarm report, how will you document this false alarm?

You could use software to create a reassessment report to be able to release the product. Or better yet, choose a data logger that has an Alarming ON/OFF function that you can use to pause the alarming. In a case like this, the data is still being logged in the background and the start/stop is clearly outlined on the PDF report.

Consider: *You have new receiving sites and unsure of their capabilities.*

Ultimately, to achieve an uninterrupted successful cryo shipment, you need to ensure easy access to the data. The simplest and most straightforward way is to see the alarm on an LCD screen that allows a quick 'go/no go' decision for the receiver. As we will discuss later, wireless data transmission is also possible to get a read-out, but with real-time devices, software is needed to read-out. A modern USB data logger is simply plugged into a computer and generates a PDF with embedded raw data, with no need for special software.

Your other consideration for new sites may be ensuring you get the data back. In other words, ensuring you are documenting the compliance of that shipment to be within temperature specification. It's important to save those reports for auditors, and the most full proof way is in a central database or cloud archive that is 21 CFR Part 11 and Data Integrity compliant.

High/Low Peaks Data on Aircraft

With cryo shipments, temperature low and high peaks can correspond with flight movements. In cryo tanks of various manufacturers and vendors, during flight the temperature can drop shortly after takeoff and can rise shortly before landing compared to the steady temperatures during the rest of the shipment.

These high/low peaks are explained by the barometric pressure differences experienced in the plane after takeoff and before landing. You will usually see this in an international shipment due to the elevation they fly at.

Some studies have shown the overall temperatures could vary from -165 °C to -196 °C.

Possible explanations could be the LN2 charge of the dry shipper could be low, or the sensor is mounted improperly and measuring the wrong area inside the tank.

To fully evaluate if the mounting was the issue, you should contact your service provide to do a full system calibration of the unit.

Wireless data

Today there are many choices for monitoring your valuable biopharmaceuticals wirelessly. Bluetooth Low Energy (BLE), GSM enabled devices, 'smart' boxes and more. USB data loggers still tend to be the standard for cryo, but there is certainly a lot of interest and movement toward real-time monitoring for greater visibility into product movement around the globe, such as proactive information in case of temperature excursion.

So how do you decide which type of monitoring is right for your product? How do you know if you need to make a higher investment in real-time hardware and software? Most often, the evaluation includes shipping lane risk, value of product, mode of transport and shelf-life of product, as well as time savings and increase of quality in the overall process.

However, each company or person's decision-making around this is different. It's like choosing your next car – quite a subjective decision.

Questions to consider in your process

1. Is your monitoring using button-cell batteries that are DGR exempt from declaration to ensure no delays in your irreplaceable shipment?
2. Can your data logging be interrupted, alarming turned on and off, if LN2 needs to be refilled while in-transit? Better yet, does your monitor have a 'pause' button?
3. Is every piece of your cryo vessel system properly installed, calibrated and qualified as a unit?
4. Is your logistics service provider the best provider to maintain and ensure full cryo system functioning?
5. Look for an integrated solution, whereby the logger, bracket and mounting are all done by the same provider to ensure a robust integrated monitoring solution.

Example of wireless monitoring Smartphone app providing critical pieces of data

10 Lessons Shipping Cryo

1. Ensure your monitoring device is calibrated according to ISO 17025 on a regular schedule.
2. Get your full cryo shipping system calibrated annually by ISO 17025 accredited laboratory.
3. Ensure the mounting of the probe uses proper sealant, usually down by a qualified specialist.
4. In case of mishandling or false stops, ensure your data logger is still collecting data in the background.
5. Choose best in class monitoring with memory capacity (75,500 values) and battery life gives you confidence that longer shipment or application durations are always monitored.
6. Use a monitoring that has functionality of a "pause alarm" button that saves time during processes like refilling cryo tanks, with actions are fully documented on your PDF reports.
7. Consider wireless monitoring to speed up data retrieval and product release.
8. Ensure your monitoring and shipment reports are archived safely somewhere should a regulator come to audit.
9. Start simple and cautiously evaluate where to implement software features, e.g. for automation purpose.
10. Choose best in class monitoring solution that is fully validated according GDP/GMP requirements.

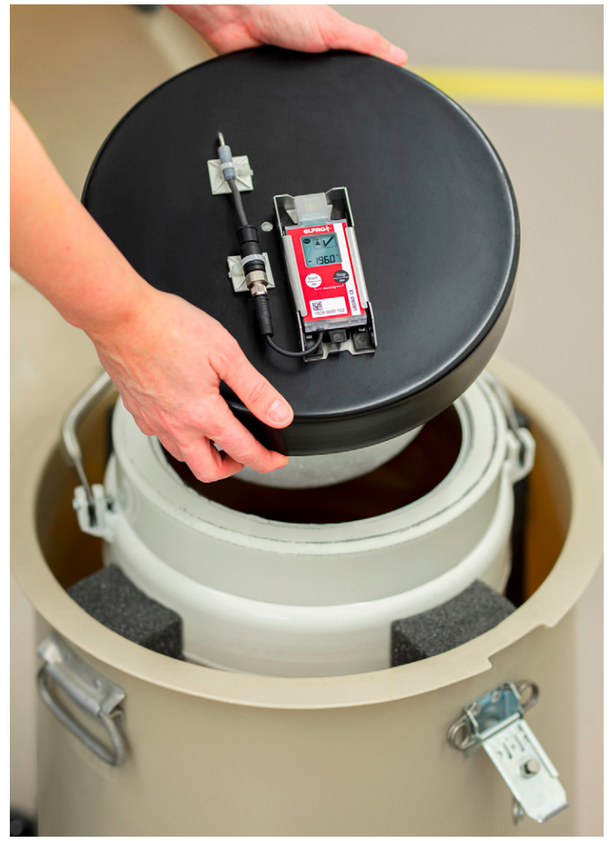
Conclusion

Cryo isn't as easy as it used to be. There is more pressure on manufacturers and their transport partners to ensure these life-saving, and valuable biological materials are handled properly.

Data can prove your product or materials can be released and safe to use – making regulators happy, and your investors. Data management tools are also key in gaining visibility in your cryo supply chain and taking control of it. Your patients are relying on your safeguarded and efficient supply chain!

Contact ELPRO to learn more on this subject and how LIBERO CE (data logger) and liberoMANAGER (cloud database solution) can help ensure solid processes for your cryo supply chain. LIBERO CE has been hailed as the 'best in class' cryo solution available on the market for it's high accuracy and robust monitoring system throughout any mode supply chain. Features like the ON/OFF alarming button help to drastically simplify processes.

Pharma companies trust ELPRO to help them ship human cells in cryogenic containers worldwide.



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