BIOTECH

Technical Report

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Bringing the Freezing of Biopharmaceuticals in From the Cold

Integrated Solutions To Minimize Risk and Preserve Product Quality

Introduction

Do we dare treat drug substance freezing as an isolated process? Or should freezing be integrated with bulk filling, storage, shipping, thawing and fill-finish operations to deliver a multi-site end-to-end process that is inherently seamless and equally capable of assuring consistent product quality and safeguarding valuable product?

The Increasing Need for Freezing Biopharmaceutical Product

With 59.4%[1] of manufactured drug substances being in a frozen state prior to shipping, it is not surprising that over recent years freeze-thaw technology has been scrutinized for efficiency, not only for the physical act of freezing and the effect it may have, but also the processes surrounding it – filling, storing, transporting, thawing and traceability. It is paramount that high value product – both in terms of money and patient safety – is given priority so that it can reach patients quickly, while maintaining the safety, efficacy and activity profile, using economically sound processes and technologies. With this in mind, the conventional static freezing methods need to be weighed against the potential advantages of alternative approaches such as plate freezing technology.

Static vs Plate Freezing

Freezing of bulk biopharmaceuticals has traditionally been achieved with static blast freezers. These, despite the expectation from the term 'blast', tend to achieve relatively slow freezing rates, and are characterized by differing freezing rates throughout the bulk of the liquid product. Freezing processes transfer heat from the fluid via the surface of the container. Slow freezing, where the method leads to a slow transfer of heat and a freezing geometry with a low external area to volume ratio, can cause compression of the core volume by the slowly advancing solid phase and lead to potential damage to sensitive solutes, such as complex proteins, in the bulk. Cryoconcentration, a phenomenon caused by differential solubilities between the solid and liquid phases, is also more prevalent when slower freezing technology is utilized and can lead to unwelcome degradation of actives at these localized elevated concentrations. Generally, slower freezing has a greater impact on drug substance quality when compared with faster freezing technology.

Plate freezers on the other hand are characterized by relatively rapid product freezing, a process which inherently reduces the extent of cryoconcentration. When coupled with containers with a high area to volume ratio such as a 2D single-use biocontainers, efficient freezing is achieved through, faster, direct heat transfer with the plates, with simultaneous freezing of both sides of the biocontainer. The result is a freezing process with more controllable freezing kinetics which largely prevents compression of the core and the type of damage seen with traditional static freezing methods.

A rapid freezing process ensures homogeneity and is especially important for products such as vaccines, monoclonal antibodies (mAbs) and viral vectors, where consistent quality, activity and stability are the highest priority. Rapid freezing minimizes crystallization, reducing the potential for contamination and product loss from precipitation.

The Effect of Cryoconcentration

So, what exactly is cryoconcentration and how does it affect drug substances during the freezing process?

Cryoconcentration is a naturally occurring phenomenon driven by differences in solubility of a component at different temperatures and in different phases. Generally, solubility decreases as temperature decreases and as ice crystals gradually begin to form during the freezing process any solutes and active ingredients within the liquid become excluded from the forming crystals. This is freezing rate dependent and therefore for systems where this rate is varied, such as slow freezing using containers with a low surface area to volume ratio, the result is a loss of drug substance homogeneity with concentrations of the active material and other solutes becoming 'trapped' within pockets of the liquid phase of the partially frozen mixture. Faster freezing reduces the solubility gradient as the rate of diffusion of the solutes away from the advancing solid phase, is slower than the rate of growth of the solid phase, trapping the solutes in the crystals as they form. Freeze rate is therefore an important parameter to assess when developing suitable steps within a process.

Figure 1: *Cryoconcentration observed in blast (A) and plate (B) freezers using naphthol blue black color agent*

A. *Blast freezer 'slow freezing' - Dark spots indicating a higher cryoconcentration*

B. *Plate freezer 'fast freezing' - Homogenous freezing (no dark spots) indicating cryoconcentration is significantly reduced*

It is not only homogeneity that is affected, a formulation change such as a change in localized pH, can give rise to chemical degradation of active ingredients as well as aggregation and precipitation. In addition, cryoconcentration has the potential to cause denaturation, whereby proteins can lose their structure and functionality; an undesirable effect when consistency in product homogeneity and product activity is the end goal.

Studies have also shown that a slow thaw rate has an effect too, with recrystallization becoming more prominent and small ice crystals becoming larger resulting in the potential for protein damage to occur as they shear on the ice-liquid interface[2].

Experiments by Lashmar, Vanderburgh and Little, conducted to evaluate the effects of the freeze-thaw process on active ingredients within a mAb formulation, confirmed that there was an inverse relationship between cryoconcentration and the Freeze Front Velocity (FFV).

FREEZE FRONT VELOCITY (FFV)

A measure of how quickly the content of a container is frozen.

(Calculated by the distance that an ice front has to travel to completely freeze the content of a container over the time it takes to freeze).

Although there are a number of parameters that have the potential to degrade an active ingredient/product, it is very clear that reducing cryoconcentration during freezing in turn reduces adverse effects on a drug substance. Controlling, and ideally reducing or eliminating cryoconcentration is key to maintaining product quality post-thawing.

Modern Freeze-Thaw Technology: What Does It Offer?

In response to the growing needs of the biopharmaceutical industry, modern freeze-thaw technology has evolved to deliver better control through automation and configuration of the freezing process. Three main problem areas have been addressed.

Firstly, and above all, biopharma's main freeze-thaw need has been, and always will be, the preservation of the quality of any frozen substance. Here, the trend is towards the use of fast freezing using plate freezers as an inherently rapid freezing technology.

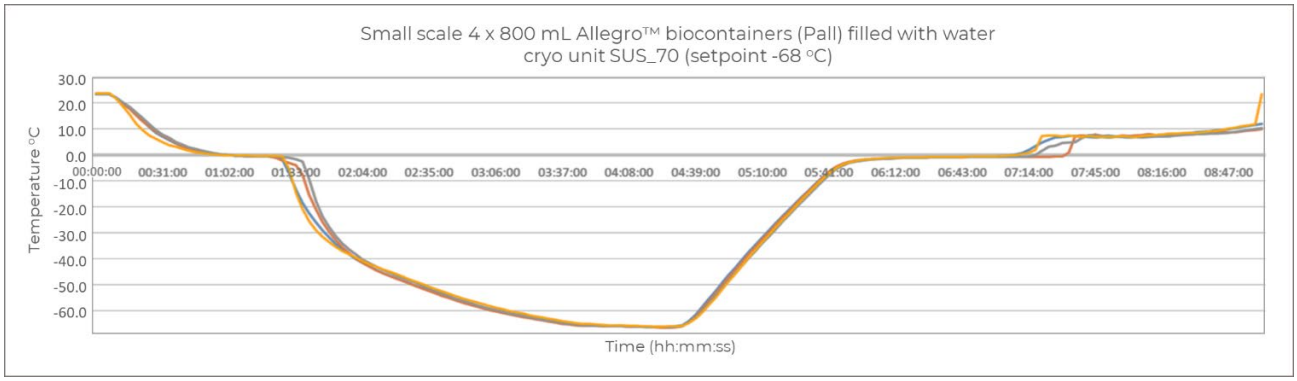
Secondly, with the continued drive for single-use solutions across all process stages, the need for robust storage and transport of frozen drug substances has become paramount as the biopharmaceutical industry continues to outsource fill and finish processes to specialized contract manufacturing organizations (CMOs) that are in increasing demand around the world. With the regulatory scrutiny that accompany all clinical drugs, these robust storage and shipping solutions have become increasingly organized, providing complete traceability throughout a temperature-controlled, and monitored cold chain.

Lastly, scalability has been addressed with modern solutions having the capacity to freeze a full range of volumes and quantities. Highly consistent freeze-thaw platform technology has the flexibility to manage both the individuality of small lab-scale batches and the substantial volume requirements of bulk manufacturing.

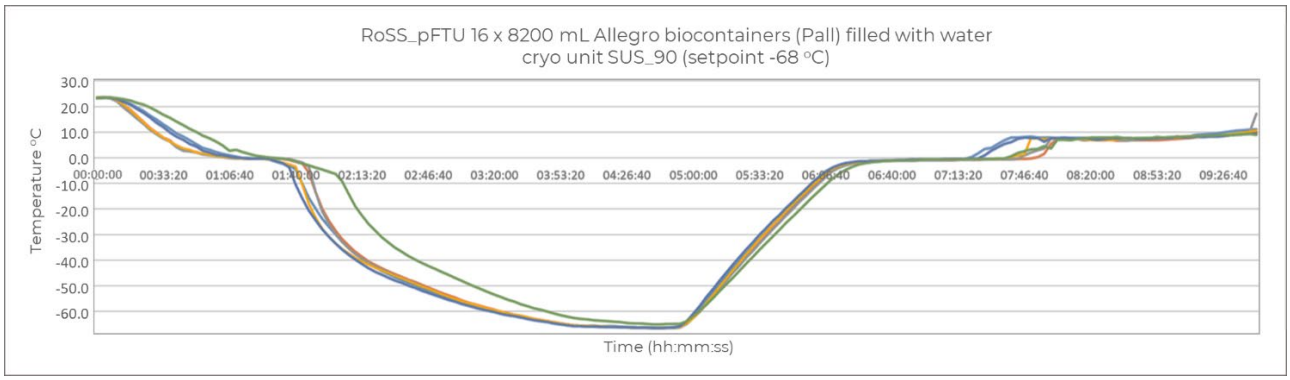
The curves below highlight how modern freeze-thaw technology, such as the RoSS.pFTU Freeze Thaw Platform, has virtually identical freezing kinetics whether freezing at lab scale (3 L) or more commercialized quantities (300 L).

Figure 2: *Examples of freeze-thaw curves of a fully scalable process*

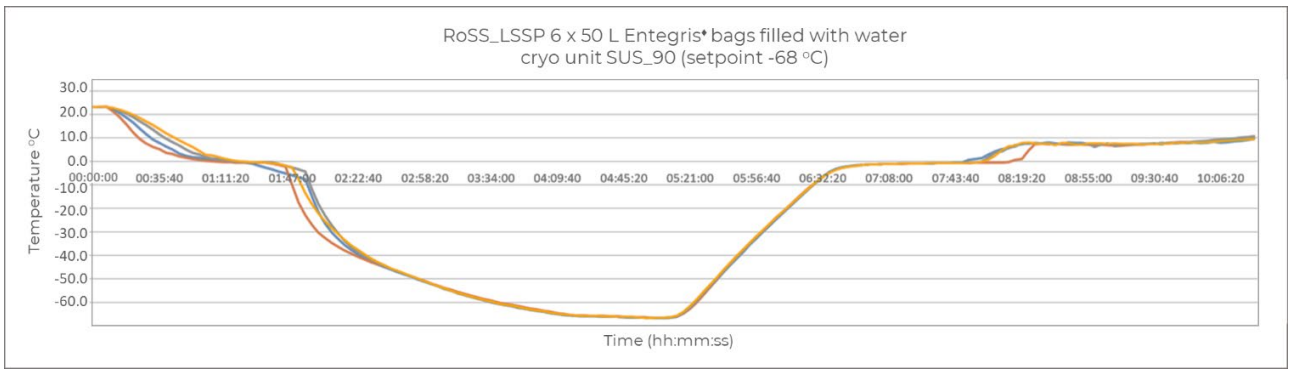
A. *Lab scale drug substance freezing (3 L)*



B. *Scale up drug substance freezing (150 L)*



C. *Commercial batch size drug substance freezing (300 L)*



Additional Benefits of Modern Freeze-Thaw Solutions

Rapid freezing and the generation of homogenous frozen solutions with a consistent product quality profile are not the only advantages. Modern solutions also have the advantage of:

- Minimizing production costs through process streamlining
- Maximizing production agility through the inherent scalability and efficiency of single-use technology
- Significantly reducing the need for cleaning and sterilization through the adoption of single-use technology
- Reducing the environmental impact of the process through reduced power and water consumption

Fill and Finish: The Necessity for Robust Storage and Shipping

With the need for specialized facilities and hardware, fill and finish processes have long been outsourced by biotech companies, but recent years have seen a rise in use of CMOs for these final manufacturing processes. Research has highlighted that around 96% of companies outsource at least some of their fill and finish needs to CMOs[3]. This clearly highlights the need for robust storage and shipping solutions to allow for safe transport of highly valuable drug substances between sites and often between countries.

REASONS FOR ENGAGEMENT WITH CONTRACT MANUFACTURING ORGANIZATIONS

- Lack of in-house capacity
- Lower supply chain risks
- Sudden unexpected demand
- Specialized manufacturing requirements
- Mandatory second sourcing policies
- A need to produce novel product formats

Although engagement with specialized CMOs is not new to biomanufacturing, reasons for engagement are becoming more diverse as drug substances become increasingly innovative. However, an overriding commonality in CMO engagement is a necessity for robust storage and shipping solutions, especially when transporting high value, patient critical frozen drug substances.

What criteria characterizes a robust storage and shipping solution for frozen drug substances?

The answer is threefold:

- To maintain frozen temperatures within validated limits over a specified period
- To protect frozen product (whether in single-use biocontainers or bottles), from the rigors of transportation, by minimizing manual handling errors and reducing the impact of foreseeable physical stresses
- To provide full traceability throughout a product's journey, from leaving the manufacturing facility to final delivery

Supply chains can be complex and despite distinct improvements to supply chain visibility4 over recent years and good distribution practices being adhered to, handling damage, human error and insufficient traceability all ultimately lead to the risk of product loss.

Temperature sensitive, shelf-life dependent active substances also have the potential to degrade and ultimately it is the responsibility of the manufacturer to ensure that any packaging and shipping routes or practices are robust. As such, a pro-active biotech company will give some considerable thought to how the precious and sensitive cargo is transported and will seek innovative packaging solutions that are designed with performance, usability and scalability in mind and supported by strong data and good science.

A potential step further in the packaging of frozen product is the connection of multiple manufacturing stages in an automated, integrated process that takes bulk drug substance, fills it into suitable biocontainers that are then rapidly frozen and stored in robust packaging shells, ready for transportation. Protective shells that are continually tracked and monitored through their shipping journey before controlled thawing at their final destination using the same control that was applied during freezing.

This type of integrated solution has the potential to minimize risk and preserve product quality.

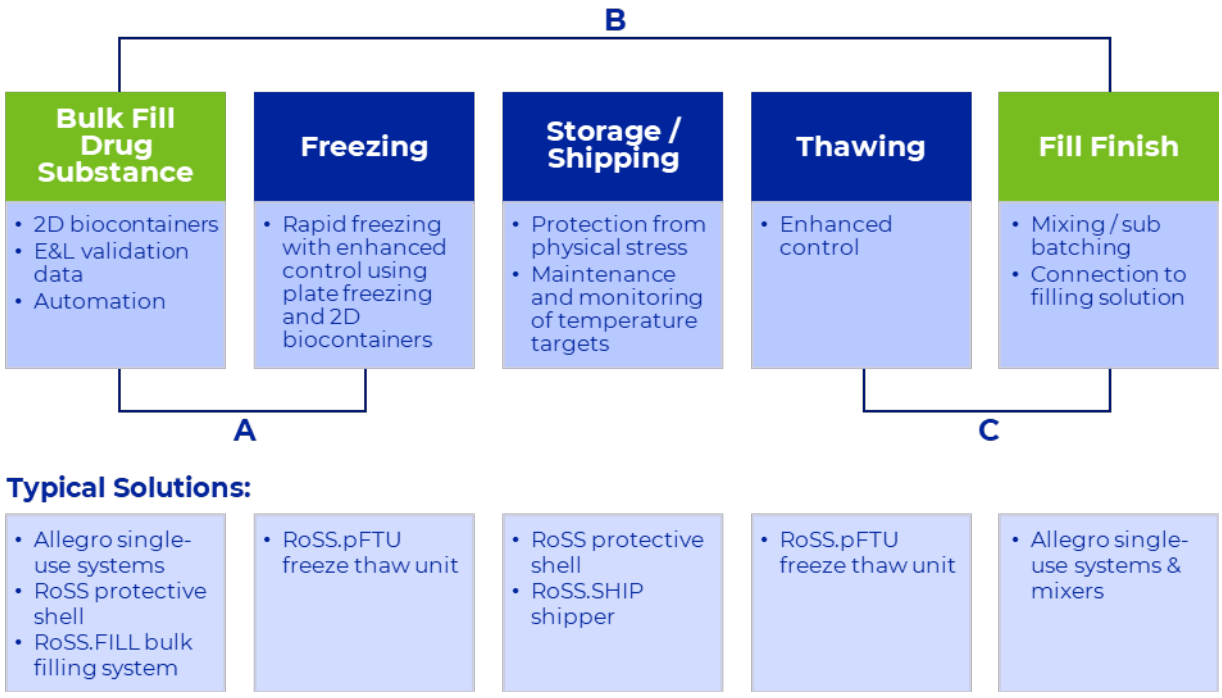
Freeze-Thaw Integrated Solutions

In the simplest of terms an end-to-end solution is a completely functional solution delivering a self -contained system, service or process stage from beginning to end. Integrated solutions are typically sourced, or managed, through a single supplier whereby ownership, and responsibility, of the supply chain for the process is focused upon a single point. When seeking integration, where a gap needs to be bridged, such as that often seen between downstream processing, the freezing of drug substances and the fill and finish stages conducted by CMOs, innovative integrated solutions are particularly advantageous, tightening up process stages that have the potential to be disjointed and sharing value to both sites through enhanced planning and process alignment.

When drug substance freezing is desired as part of a process flow, what could an integrated solution at this stage of the process look like?

An integrated solution seeks to achieve a seamless connection of interlinked process steps. In the context of freezing bulk drug substance, the steps immediately upstream and downstream of this operation needs to be considered.

Figure 3. *An integrated approach to freeze / thaw solutions*



A) The end stages of drug substance manufacture culminate in filling into the preferred containers and sterile disconnection from the process. Here, driven by the knowledge of the benefits of plate freezing, the bridge between this part of the process and the freezing drives the use of 2D biocontainers. This in turn helps define options for the automation of this filling process to streamline the process and control risk. This also provides an opportunity to build in design elements to facilitate disconnection from the filling process.

B) Validation data, specifically that referring to the extractables and leachables evaluation that forms a critical part of the assessment of the safety profile of the final drug product, can be repurposed for all materials with a common contact

surface. Specifying product contact surfaces such as those in mixing or filling systems minimizes the validation burden and reduces the potential set of leached materials in the final drug product. With the desired freezing process in mind it is advantageous to select biocontainer bags that have a low extractables profile and validation data at the target temperature, typically as low as -80°C. Additionally freeze-thaw as an end-to-end solution should encompass comprehensive transport validation reports and data that fully comply with ASTM protocol and ISTA (3E and 3H) guidelines to provide complete assurance of robustness.

C) Following controlled thawing of the bulk drug substance, the optimized design of all consumables ensures the easy, safe transfer of thawed bulk to the fill finish operations with the appropriate connection and disconnection technology, sharing the validation data for any common components used during the bulk filling.

Using these points of integration, a typical process may flow seamlessly with shared validation data and system design principles supporting high performance and robust, streamlined operations.

The combination of Pall's Allegro single-use portfolio, including biocontainers, working in harmony with Single Use Supports' RoSS♦ technologies, and managed and supplied through a single point of contact, provides peace of mind and a proven solution that integrates seamlessly with all parts of your process and at all scales as your process develops.

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