SINGLE USE SUPPORT.

PIONEERING BIOPHARMA

Freezing and storage of bulk drug substance batches

A harmonized cold chain process for high-capacity, full-batch operations

Introduction

A cold chain is often described as something continuous and well-integrated. In day-to-day biopharmaceutical manufacturing, however, the reality often looks very different.

As batch volumes increase while facilities remain unchanged, freezing and ultra-cold storage quickly become capacity-limiting steps. What once worked at a smaller scale starts to break down: freezing and storage are treated as separate unit operations, equipment is added in isolation, and workflows become increasingly fragmented. The result is additional handling steps, increased internal transport, and elevated risk.

Most inefficiencies do not originate from individual systems, but from the lack of coordination between freezing and storage steps.

This application note looks at freezing and ultra-cold storage not as isolated operations, but as a single, connected cold chain process. Considering a representative bulk batch size of approximately 200 L, it focuses on practical manufacturing realities, including multi-format primary packaging and the operational constraints typical of CDMO and multi-product environments.

How is it possible to preserve product stability while enabling the decoupling of manufacturing steps across time and site? A freeze-to-store workflow treats freezing, transfer, and ultra-cold storage steps as one continuous operation, with defined temperature control strategies and standardized handling logic, across all process steps.

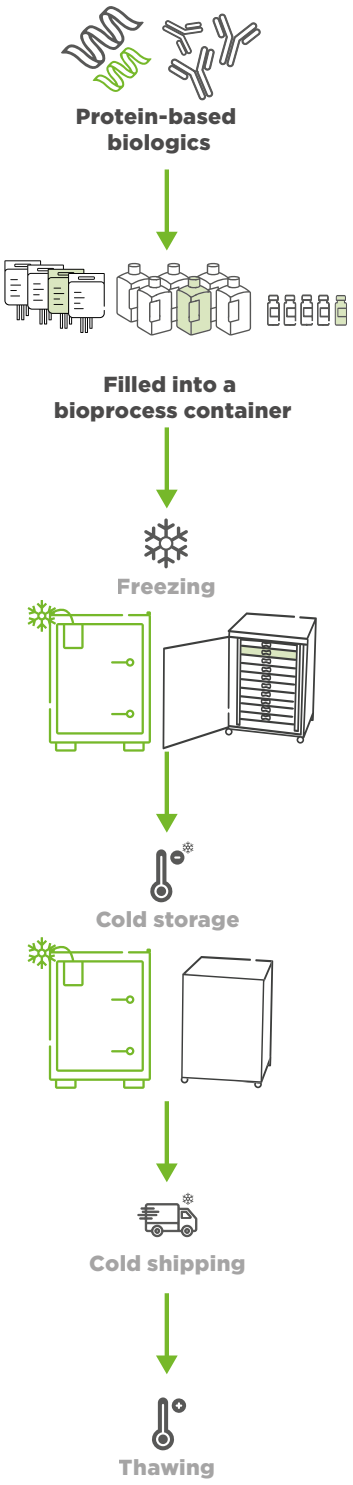


Figure 1: Single Use Support's plate-based freeze-thaw platform for single-use bags

Biggest challenges in cold chain operations

Not coordinated

In many biopharmaceutical facilities, freezing and ultra-cold storage are still not coordinated as batch-level process steps. Instead, freezing and storage are often planned independently, without a clear batch concept that spans both operations. As batch sizes increase and variability grows, this lack of coordination becomes increasingly apparent and directly limits scalability. One direct consequence is the complexity of storage logistics. A single frozen batch is often divided and distributed across multiple storage freezers because freezing capacity, storage capacity, and internal space utilization are not aligned. This results in so-called “empty miles” within facilities: unnecessary internal transport and additional handling steps.

Improper use of equipment

Static ultra-low temperature freezers, designed for long-term storage of already frozen material, are often incorrectly used to actively cool or freeze bulk drug substances (BDS). This leads to extended and uncontrolled freezing times, increases the risk of cryoconcentration, and can negatively impact product integrity and batch-to-batch reproducibility.

Poor space utilization

Cold chain inefficiencies are further amplified by poor space utilization. Freezing and storage equipment is often loosely fitted to the available footprint, resulting in underutilized capacity. A more integrated, batch-oriented approach would allow existing space to be used more efficiently, reducing the equipment needed, operator time, and overall energy consumption, while supporting sustainability goals.

Locked-in

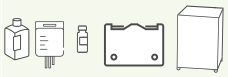
When freezing and storage concepts depend on a single container type or supplier-specific ecosystem, operational flexibility is lost. This technical lock-in is particularly critical for CDMOs, which must support multiple customer-specific primary packaging formats. True multi-format compatibility across bags, bottles, and other containers is essential for maintaining operational flexibility without compromising freezing performance, product protection, or storage strategy.

Figure 2: Frozen drug substance handling in single-use bags can be manual or supported by full-batch processes

Freezing and storage of BDS batches

Static, plate, or blast freezing in bulk operations?

Different freezing concepts serve distinct operational purposes in the biopharmaceutical manufacturing of BDS.

	Technology	Suitability with primary packaging	Speed	Probability of cryoconcentration	Variability	Best for
Static freezer	Natural convection		Slow[1]	High	High[1]	Storage
Blast freezer	Forced air convection (fans)		Fast	Low (if controlled)	Medium to low	Freezing
Plate freezer	Direct conduction (plates)		Fast	Low (if controlled)	Low	Freezing

Static freezing relies on passive heat removal and is typically associated with storage freezers. While simple to operate, static systems are not designed to cool drug substances as they offer limited control over freezing kinetics and often lead to high variability within the loaded bags or bottles.

Plate freezing enables efficient heat transfer through direct contact and is commonly used for flat, 2D, single-use bag formats. Its suitability is heavily dependent on container geometry and process integration.

Blast freezing uses forced air convection to actively enhance heat transfer around containers. In bulk drug substance operations, blast freezing is particularly relevant when several single-use bioprocess container formats are used. Controlled airflow can improve freezing uniformity and reduce freeze-thaw cycle variability. When integrated into a defined workflow, blast freezing supports predictable, repeatable freezing at scale.

Figure 3: Single-use bottles are typically frozen in blast freezers (l.), while single-use bags are often frozen in plate freezers (r.)

1. Feigl C.: Process Development for Controlled Freezing of CHO Cells. 2025. Master's Thesis

Best practice for controlled freezing with RoSS.BLST

Controlled freezing at bulk scale requires predictable cooling of the drug substance in single-use primary packaging as well as consistent execution of defined freezing profiles. RoSS.BLST supports these requirements through recipe-driven operation and batch-oriented loading concepts.

By standardizing freezing cycles, RoSS.BLST reduces run-to-run variability and supports reproducible freezing behavior across different container types. This is particularly relevant when managing batch volumes of up to 250 L across mixed primary packaging formats, where uniform thermal exposure is essential to ensure process robustness. **Efficient cold air circulation across the entire chamber enables homogeneous freezing of substances while achieving reduced run times.**

RoSS.BLST is designed to offer a best-in-class ratio of chamber volume to overall footprint, enabling efficient use of available space. Despite its compact footprint, the system integrates easily into space-constrained environments while still providing a generous chamber volume. As illustrated in Fig.4, Single Use Support's blast freezer is approximately **30% more space-efficient than other comparable blast freezing systems.**

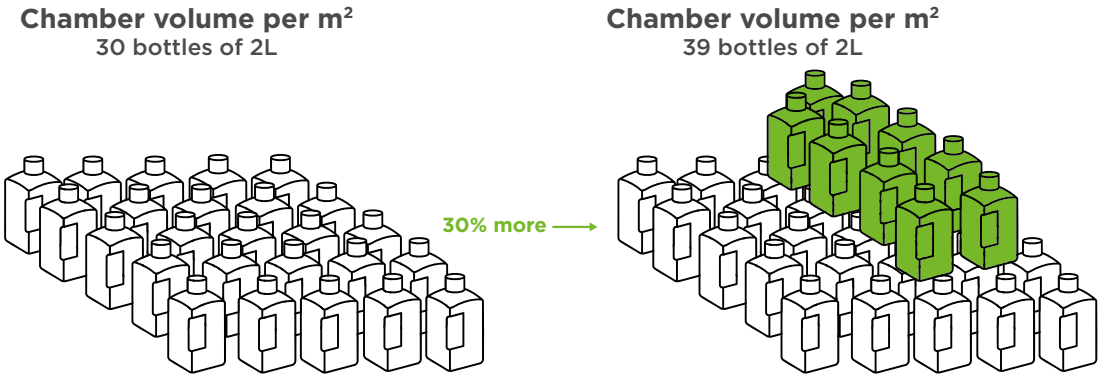


Figure 4: Space-efficient blast freezing with RoSS.BLST

Figure 5: Modular interior with shelves or full trolleys with RoSS.BLST controlled freezing of bottles and bags.

Best practice for ultra-cold storage with RoSS.ULTF

Ultra-cold storage efficiency is determined not only by temperature performance but also by usable volume, internal organization, and transfer logic. RoSS.ULTF is designed to bridge the gap between conventional static freezers and large, walk-in cold rooms, providing high-density storage optimized for BDS.

Modular & efficient storage of drug substances in different volumes at ultra-low temperatures

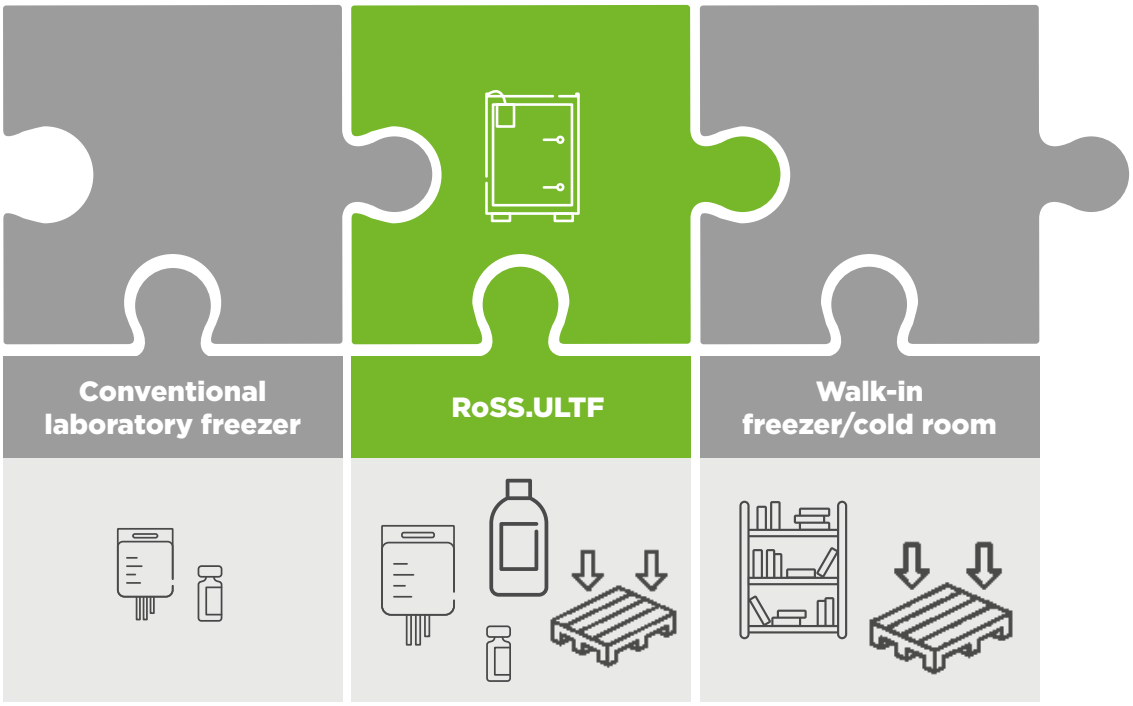


Figure 6: RoSS.ULTF as a missing puzzle piece for frozen storage of batches of up to 250 L in bags and bottles

It's one of a kind, being capable of storing complete frozen batches without splitting, reducing internal transport steps, and simplifying inventory management. RoSS.ULTF's modular internal configurations enable efficient use of the available chamber volume, while maintaining accessibility for routine operations.

Consistent electronic documentation of storage conditions and inventory movements supports audit readiness and data integrity throughout long-term storage operations.

Figure 7: The RoSS.ULTF ultra-low temperature storage freezer

Matching freezing and storage freezers for maximum efficiency in batch handling

Blast freezers and ultra-low temperature storage freezers are purpose-built systems – one designed for controlled freezing and thawing, the other for consistent ultra-cold storage. But the real value for batch handling is how they work together. **Because both freezers are fully compatible in terms of volume and handling, they enable a harmonized cold chain workflow for full-batch processing.**

Designing freezing and ultra-cold storage with RoSS.BLST and RoSS.ULTF as a single, unified process:

- Improves product consistency through reproducible freezing behavior
- Reduces manual handling, contamination risk, and deviation potential
- Supports scalable operations without expanding facility footprint

Frozen drug substance can be transferred to storage using **mobile transport racks** that are placed directly inside the RoSS.BLST freeze-thaw chamber. These racks safely carry single-use bags or other bioprocess containers during blast freezing and enable direct transfer into RoSS.ULTF, supporting straight-in and straight-out movement without the need to use a forklift. Integrated wheels or low-profile rollers eliminate additional handling steps and simplify internal logistics.

Format flexibility allows manufacturers to accommodate customer- or process-specific primary packaging formats without introducing parallel workflows or additional equipment requirements.

From a quality and compliance perspective, a unified freeze-to-store workflow enables consistent electronic record generation across freezing and storage, supporting GMP-compliant documentation and batch review aligned with 21 CFR Part 11 expectations.

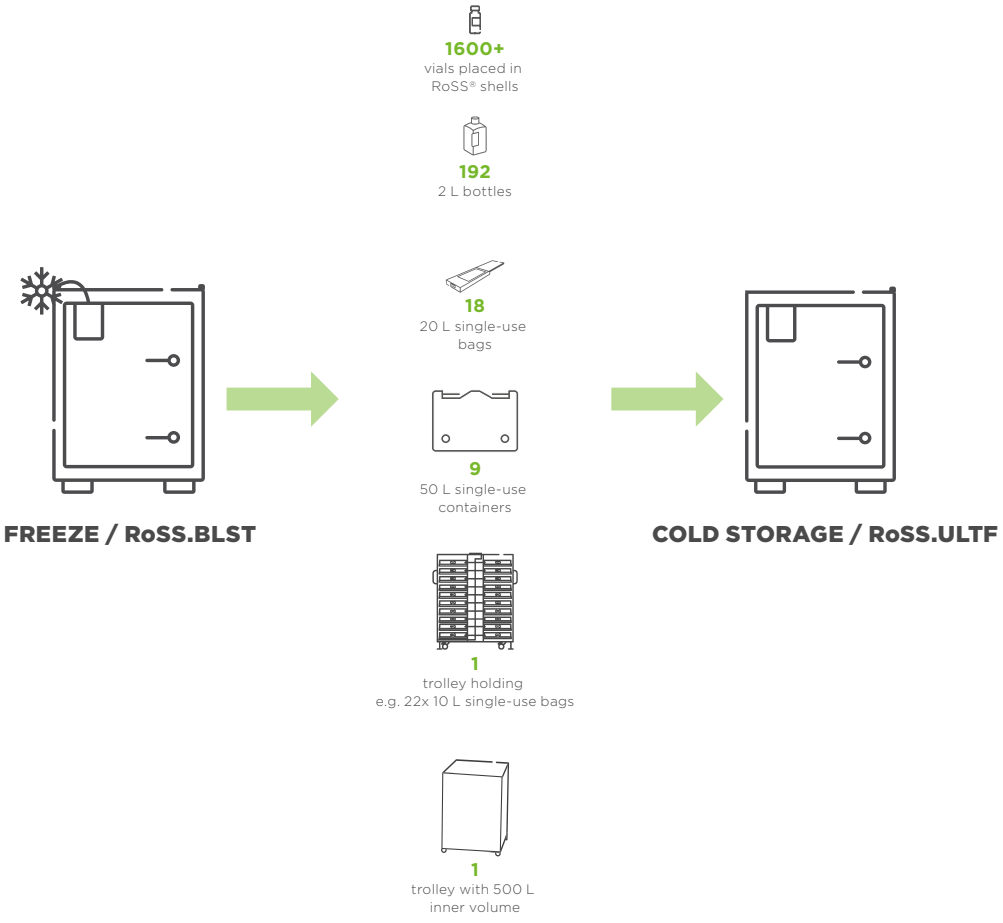


Figure 8: Freezing and storage capacity with multi-format single-use bioprocess containers at different scales

Efficiency gains with freeze-to-store batch processes

There are obvious cost elements, such as capital expenditure (CAPEX) for equipment, but the greatest cost drivers in bulk freezing and storage operations are rarely the equipment itself.

Operational expenditures (OPEX) have a significant impact on the total cost of ownership (TCO) too.

These ongoing operational costs include:

- Personnel time
- Energy consumption, including water and electricity
- Maintenance
- Facility space
- The cost of deviations and losses, such as product loss due to bag breakage or compromised product quality

The freeze-to-store cold chain directly impacts all of these cost drivers - not only equipment-related costs. It influences process efficiency, resource consumption, product integrity, and operational risk, making it a critical lever for controlling TCO.

When freezing and ultra-cold storage are designed as one single, integrated process using RoSS.BLST and RoSS.ULTF, efficiency gains become measurable at the batch level.

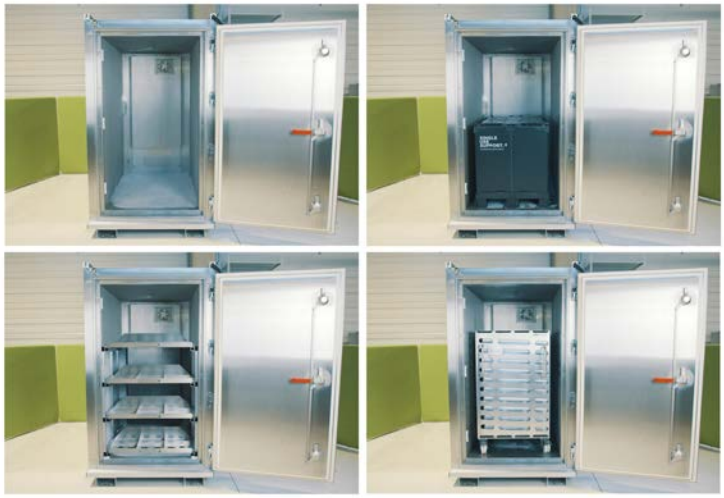


Figure 9: The modular interior of RoSS.BLST and RoSS.ULTF results in process flexibility in biomanufacturing

- **Complete batches of up to 250 L can be frozen and stored without splitting,** minimizing internal movements and handling steps. In practice, this can translate into ***30–50% fewer manual handling actions***, directly reducing operator time and lowering deviation risk.

- There is also substantial improvement in **capacity utilization**. Aligning the freezing output of RoSS.BLST with the storage capacity of RoSS.ULTF enables high-density storage of full batches, which reduces the total number of storage units required. Facilities can achieve ***up to 30% more batch capacity within the same footprint***, avoiding the need for cold-room expansion or additional freezer installations.

- **Process time** is another relevant factor. Controlled, high-capacity freezing in RoSS.BLST shortens and standardizes freezing cycles compared with static approaches, while direct transfer into RoSS.ULTF removes non-value-adding waiting times between process steps.

- **Energy and operational efficiency** also benefit from this alignment. Greater chamber utilization and elimination of partially filled units can reduce the energy consumption per liter stored, while fewer active units reduce maintenance efforts and service demand.

- Finally, the unified workflow supports consistent electronic record-keeping across freezing and storage, aligned with 21 CFR Part 11 expectations. This reduces documentation effort and simplifies batch record review, particularly in multi-batch production.

The result is a cold chain process that is not only more controlled but also more efficient, that delivers higher throughput, improved space utilization, and reduced operational complexity within existing infrastructure.

“Batch perfect” with Single Use Support

RoSS.BLST and RoSS.ULTF are complementary technologies within a connected bulk cold chain, together enabling batch-centric freezing and ultra-cold storage workflows that scale efficiently within fixed infrastructure conditions.

Additional Single Use Support technologies can be seamlessly integrated into the overall handling concept where required as part of an extended cold chain strategy. These include protection solutions for 2D single-use bags using the RoSS® shell; single-use bottles using Bottle RoSS; and RoSS.SHIP, which is used as a container solution for cold shipments. Together, they enable a consistent, end-to-end approach to batch handling throughout freezing, storage, and transport processes.

Reducing handling steps directly decreases operator involvement, lowers contamination risk, and reduces the likelihood of deviation.

Figure 10: Full-batch handling from freezing to storage with Single Use Support