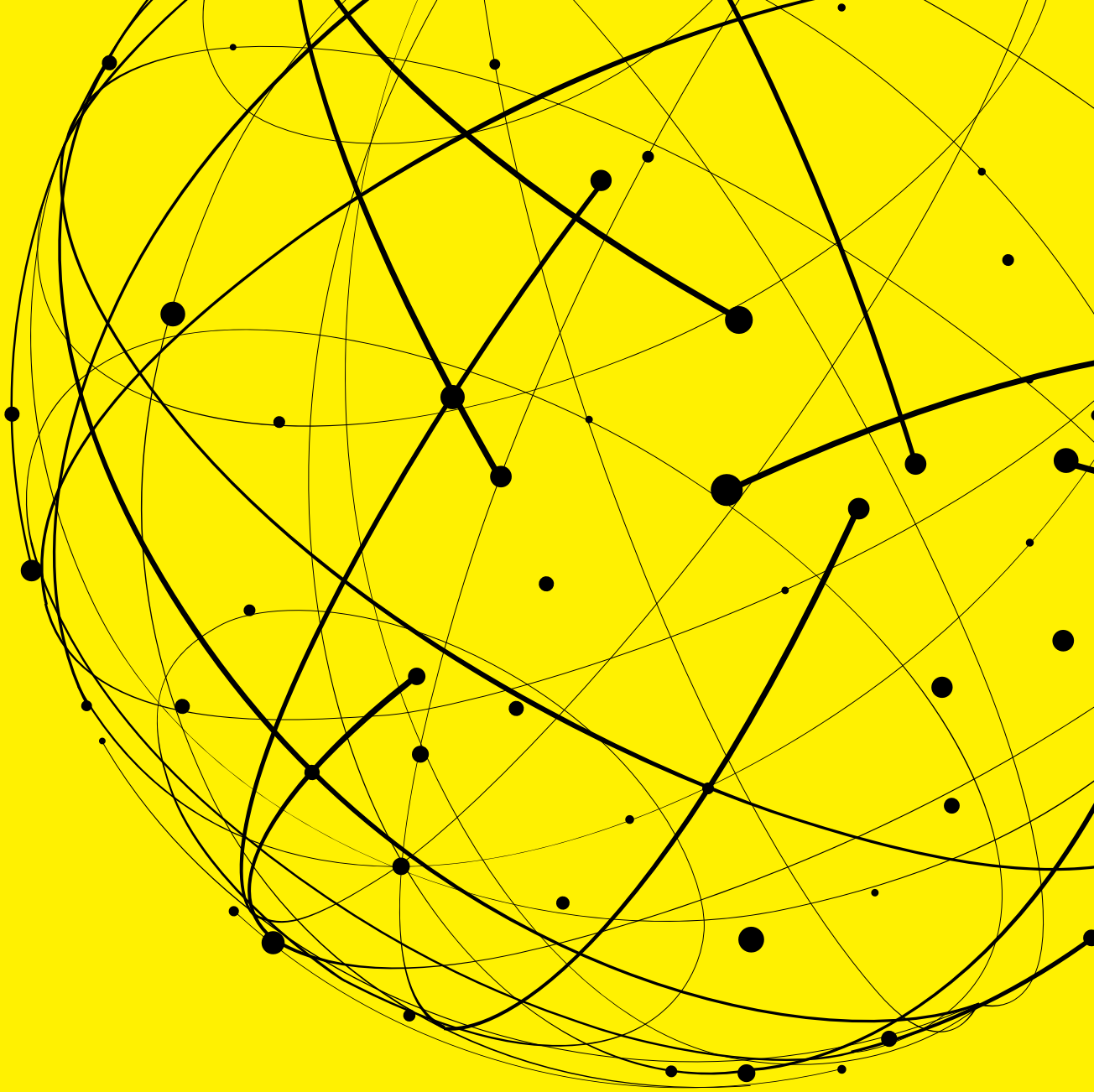

Simplifying Progress

# Managing Frozen Transport Logistics in the Biopharmaceutical Cold Chain

July 01, 2021 | Cédric Gentile, Katy McLaughlin

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Cold chain shipping, freeze thaw cycles, frozen storage, frozen transport, freeze container, freeze bags

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# Coordinating the Cold Chain

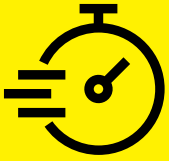
The enormous task of establishing a reliable infrastructure to supply COVID-19 vaccines across the globe has thrust cold chain shipping and its associated challenges into the spotlight. Valuable biologics, such as vaccines and recombinant therapeutic proteins, are often kept in a frozen state during storage and shipping. This requires robust solutions to ensure temperatures do not fluctuate and product integrity is preserved.

As biopharmaceutical manufacturing grows increasingly global, the production and transport networks required to keep operations running smoothly become more complex (1). Supply chains are further complicated by the trend towards decentralized production processes and the use of external contract manufacturing organizations (CMOs). The deviations associated with a complex production network can place strain on the frozen transport network.

Sartorius has extensive experience in designing and delivering innovative freeze | thaw solutions for the bioprocessing industry. Here, the authors provide a framework for making challenging decisions linked to cold chain management before outlining potential solutions that could solve many of the issues surrounding the frozen transfer of biopharmaceuticals.

## Cold Chain Solutions Should Support Trends in the Biopharmaceutical Industry

**A robust cold chain relies on secure, simple, and reliable storage | transport solutions**



**Sensitive drug substances require timely transport under secure conditions**

**Traditional freeze methods such as bottles and stainless steel tanks can be replaced by end-to-end platforms with controlled-rate technologies**

# Challenges in the Freeze | Thaw Journey

The changing product portfolio associated with the growth of the biopharmaceutical market means there is an increasing number of temperature-sensitive drugs and intermediates being manufactured, for example, mRNA vaccines (2). This evolution raises demand for platforms to support their storage, handling, and distribution.

However, biologics can be sensitive to the adverse effects of cryoconcentration and thawing, which include pH changes, redistribution of ions, protein denaturation, and phase separation. To avoid these detrimental outcomes, careful planning of the process from start to finish is essential.

The freeze | thaw journey is not universal. Biotherapeutic developers have different pressures and drivers which shape their operational strategies. As a result, their decision-making process to select the best freeze | thaw systems for their supply chain will be unique.

# Why Freeze?

There are several reasons why drug substances are maintained at cold temperatures.

Freezing facilitates longer hold periods during processing steps, boosting operational flexibility and enabling batch processing.

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Freezing the bulk drug substance limits the interaction between the product and the container, providing fewer opportunities for contamination by extractables and leachables.

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Cold temperatures can give drug substances a longer shelf life by reducing chemical | biological degradation and limiting microbial growth.

# Cold Chain Logistics

Frozen transport could be required throughout various drug development and manufacturing stages, from initial cell line development to commercial manufacturing. The general structure of the freeze | thaw lifecycle is similar for most applications and modalities (Figure 1).

Freezing during upstream processing relies on the transfer of cells from master or working cell banks for cultivation. This requires the implementation of a closed system to enable aseptic processing, the capabilities to preserve cells at ultra-low temperatures, and streamlined cold chain management. Downstream processing involves harvesting and freezing intermediates or bulk drug substance for further processing or final product preparation.

As well as requiring aseptic processing conditions and container integrity, manufacturers also need their product to be homogeneous after thawing and require the possibility of convenient logistics to remote locations.

There are different options at every step. Biopharmaceutical manufacturers must first consider how their substance will be distributed into the freeze containers and what containers will be used (e.g., bags, bottles, or tanks). Traditional, rigid containers, such as bottles and stainless-steel freeze tanks, have limitations in scalability, logistics, and reliability. On the other hand, disposable, flexible containers, if not properly protected, can pose a potential risk of failure from rupture and leakage due to stresses incurred during shipping and handling.

Manufacturers must then determine how their substance will be frozen and stored. Will they use a conventional, blast, or plate freezer? Should they employ controlled-rate or passive freeze processes? If transport is required, they must select an appropriate logistics service and ensure they have superior technologies and environmental monitoring. Decisions must also be made surrounding the thawing process. Should it be passive or controlled, and how should the liquid be drained from the container to enable further processing (for example, if not adequately homogenized before dispensing)? These decisions will depend on the biologic and the stage of its lifecycle, and are driven by the need to maintain and protect the product's critical quality attributes (CQAs).

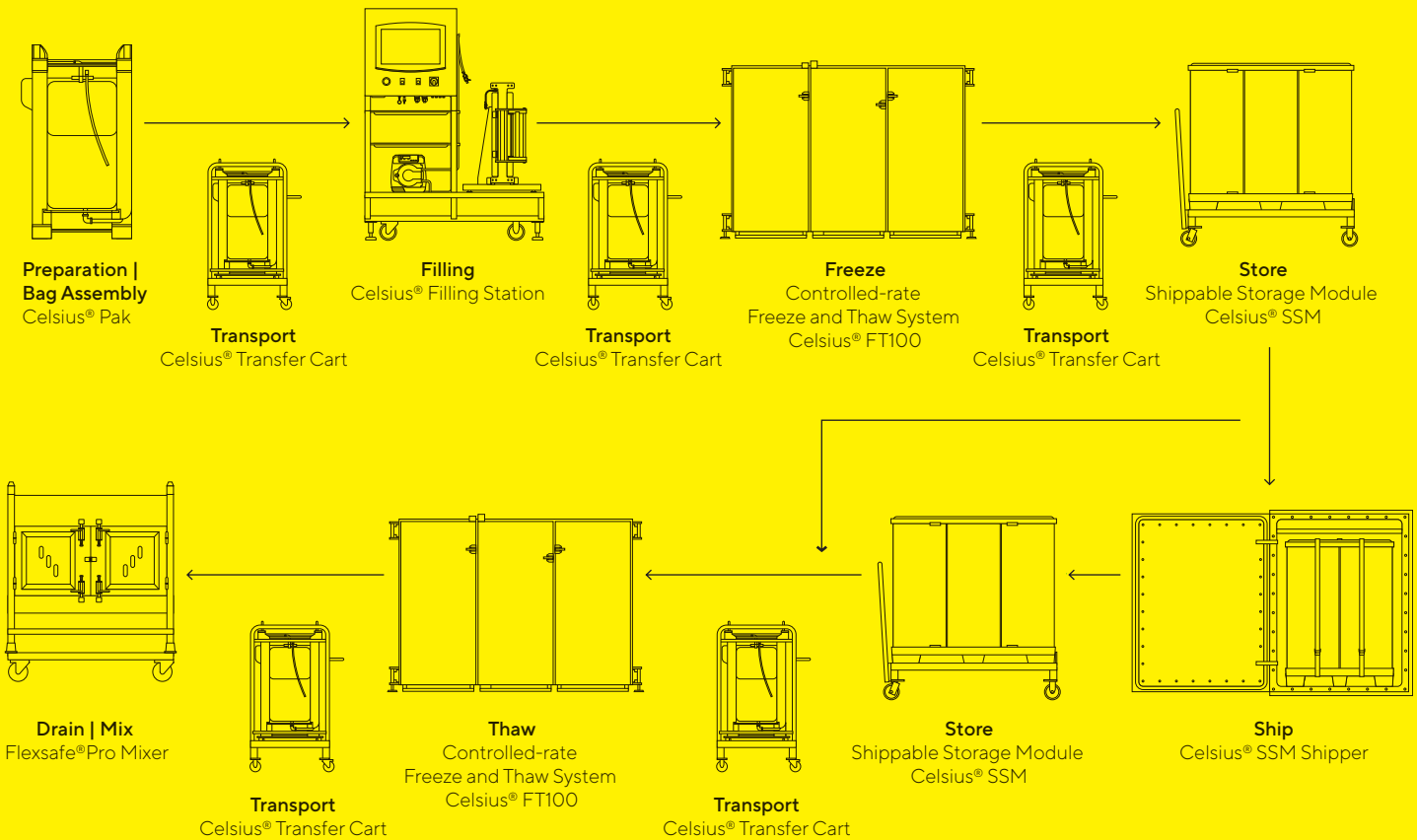
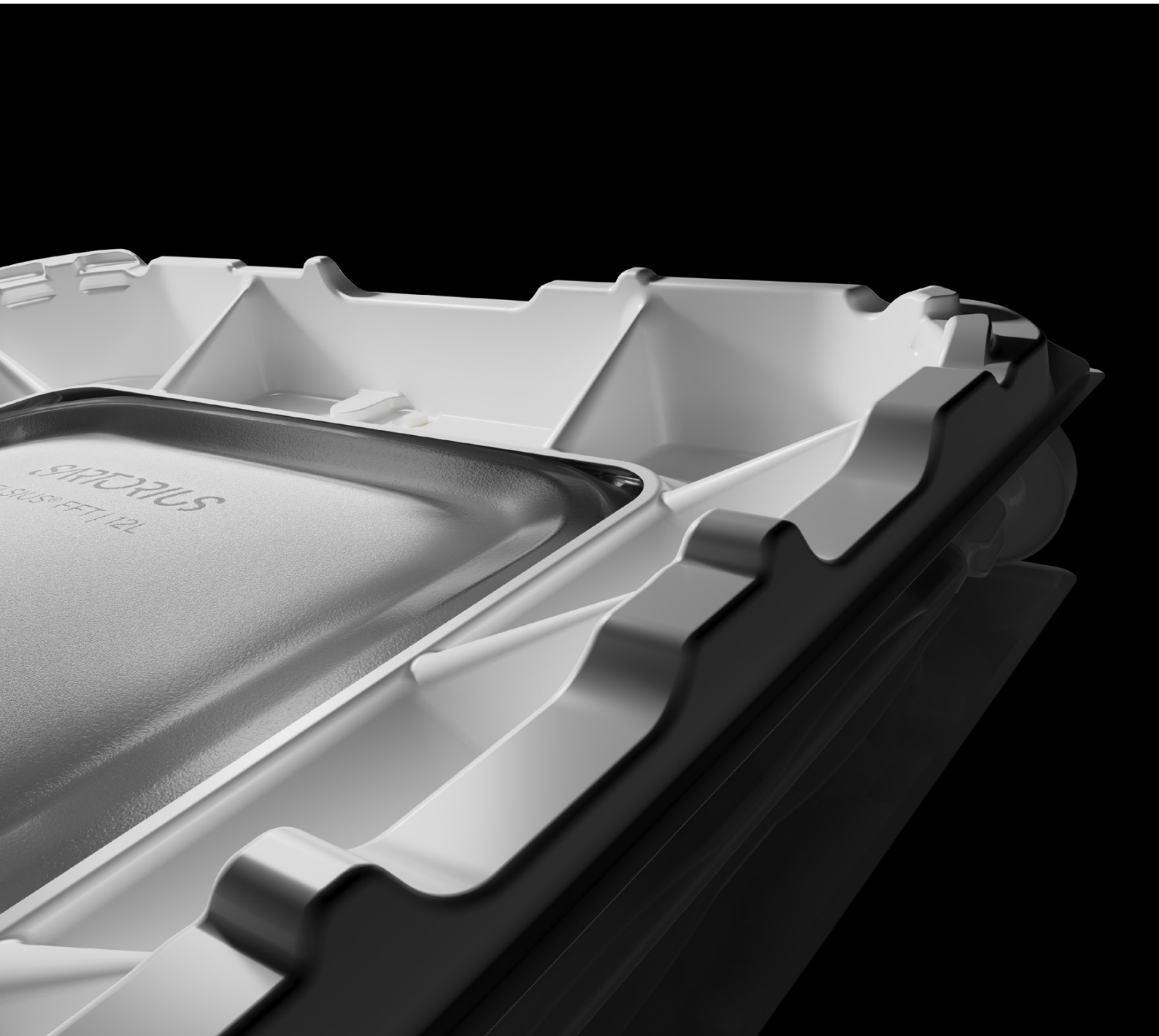



**Figure 1:** Typical steps and associated solutions in the biopharmaceutical cold chain

# A Selection Framework for Cold Chain Solutions

A poorly designed cold chain can result in disjointed relationships between steps in the supply network, leading to delays and significant losses. Biopharmaceutical manufacturers need secure and efficient freeze | thaw, storage, and transport systems to power a reliable logistics infrastructure. This requires platforms that prioritize quality, sterility, ergonomy, and simplicity, maintaining consistency across a global network.

While manufacturers' needs are broadly similar, different biologics, facilities, and developmental phases are subject to unique pressures and requirements. The process (particularly the batch size) and product (temperature requirements and process times) are the main drivers of the freeze | thaw platform decision-making. Equipment (primary) and then related containers (secondary) are also at the core of the selection process.



# Optimizing Logistics – Decision-Making Strategies

Examining the features of the above factors and how they influence individual products, organizations, stages, and production processes is essential in shaping the supply chain and the technology selection within each step. Below, we outline some critical considerations for the major drivers and potential solutions to support a robust biopharmaceutical cold chain.

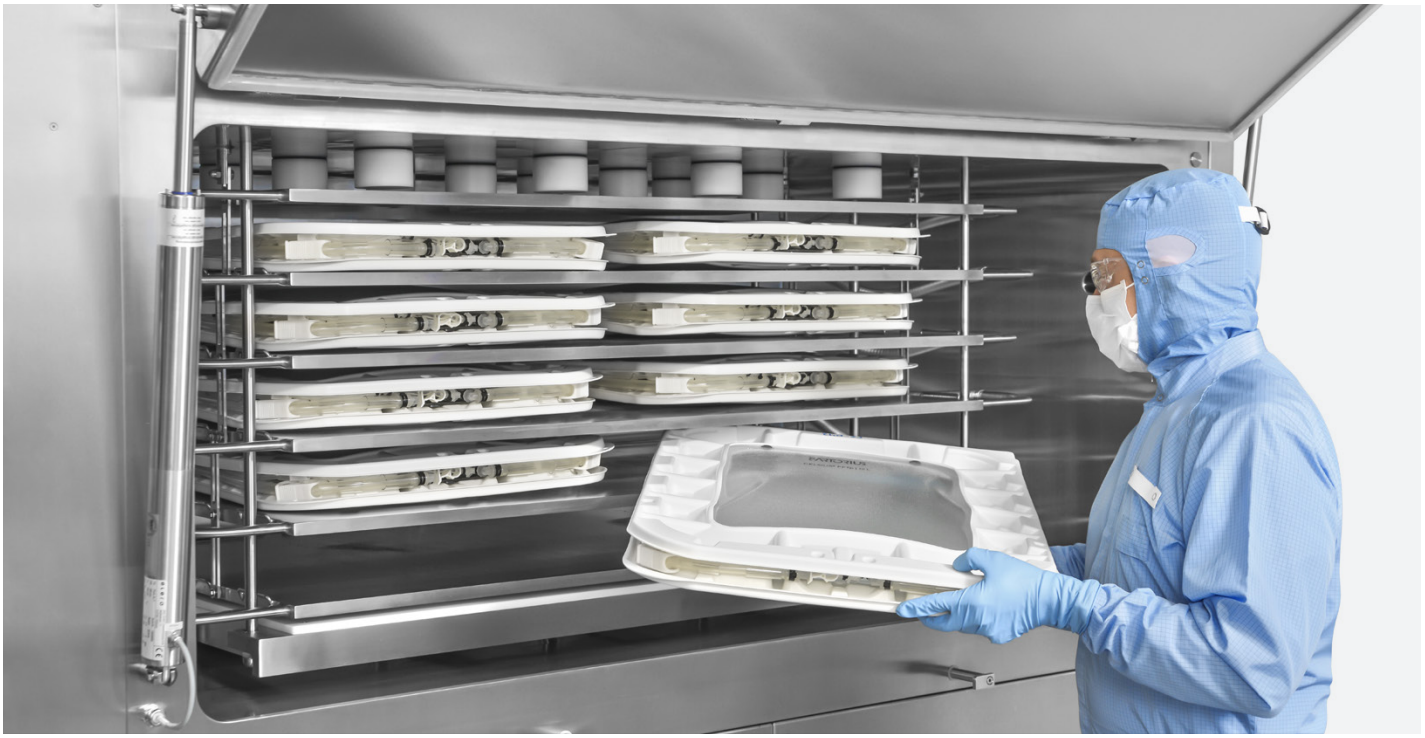
## Drivers by Biologic

Biotherapeutic products are diverse in their origin and functional characteristics. Each has distinct properties and requires unique production, transport, and storage conditions. For example, cells are typically stored and shipped in low-volume containers (around 100 mL), unlike proteins, which are transported at a range of volumes (more than 10 L in a single container).

Whereas proteins and mRNA vaccines typically require cold storage and transport at temperatures greater than -80 °C, cells are very sensitive and are usually stored at ultra-low temperatures (<-135 °C) with a specific cooling ramp to ensure cell viability. Temperature requirements are also linked to the selection of an appropriate freeze container, which must be mechanically compatible with the necessary temperature range.

Different biologics also differ in their sensitivity to cooling speed and the effects of cryoconcentration. For cells, controlled-rate freezing is not only desirable but necessary to maintain the critical quality attributes (CQAs) of the product. Living organisms such as viruses are also subject to strict shipping regulations, which will be an important consideration to avoid unforeseen delays and maintain an effective supply chain.

For cells and sensitive biologics, advanced controlled-rate freezing technologies provide the reliability needed to maintain a robust cold supply chain. Fully integrated platforms, such as the Celsius® CFT, minimize manual handling and enable full traceability across the entire freeze | thaw storage and transfer network. Investing in such established end-to-end solutions will ensure expensive biotherapeutics are maintained under optimal conditions throughout the supply chain (1).



## Drivers by Developmental Phase

During early development, speed and risk mitigation are essential, so decisions are made with the intent to decrease time-to-clinic or time-to-market. As a result, ready-to-use, end-to-end, and easily implemented freeze | thaw systems are favorable. Ideally, the selected solutions are compatible with the existing infrastructure, removing the need to install and master new instruments. The platform should also be scalable, facilitating a rapid transition to production at larger scales. The objective is to simplify cold chain logistics with one-way systems backed up by reliable qualification data (3).

For commercial manufacturing operations, cold chain decision-making is primarily influenced by the process parameters. Flexible tools that fit into existing manufacturing setups are most desirable. In some cases, manufacturers may be ready and willing to invest in the latest technologies for controlled-rate freeze | thaw. Their manufacturing needs are more extensive than early-stage developers, and they require solutions for managing and transporting large volumes through the frozen supply chain, which may include automation to reduce manual handling.

## Different Strokes

Each facility also has unique needs depending on its operations, development stage, and production capacity.

- Small start-ups are especially influenced by cost and seek to minimize expenditure by adapting their existing solutions for freeze | thaw platforms. For example, the Celsius® FFT | p is a versatile system compatible with commercially available equipment, allowing manufacturers to take advantage of the most advanced freeze and thaw solutions without the costs associated with modifying the facility infrastructure.

- Smaller, newer facilities are also the most likely to take advantage of the services offered by CMOs, requiring scalable platforms that can be easily transitioned to external sites.

- Commercial, large-scale manufacturers are driven by improving their production efficiency and managing the storage and shipping of large volumes at significant throughput.

- CMOs and distribution sites are unique in that they likely carry out diverse projects for different customers, so want to maintain flexible operations that are compatible with a variety of platforms and product types. The configurability of the Celsius® FFT | p platform is an ideal solution for facilities carrying out diverse projects.

Ultimately, biopharmaceutical companies are unique in their facility setups and do not necessarily fit into defined molds of size, scale, and capacity. Decision-making is steered by the weight each driver carries within the context of the organization. Advanced, single-use freeze | thaw technologies are designed to be adaptable to the activities of any organization, supporting reproducible freeze | thaw cycles throughout the cold chain.

# The Value of a Reliable Cold Chain

Implementing effective solutions for cold chain transport is often perceived as costly and complicated, but failures within the supply chain, including the frozen transport solutions themselves, are considerably more expensive to rectify. As we evolve more advanced therapeutics, such as mRNA vaccines and cellular therapies, solutions that support reliable cold chains will become central.

Bulk drug substances represent the culmination of an intricate series of operations requiring substantial research, resources, and time investment. However, their true value is, undeniably, in their clinical potential. Such precious material demands reliable protection during storage and transport. When evaluating the criteria of an effective frozen storage platform, product security is central. Careful consideration of the needs and drivers for each application ensures the best solution is selected for the manufacturer's cold chain needs.

# Author Bio

**Cédric Gentile**
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Cédric has been working for Sartorius since 2011, where today he is Head of Product Management for Freeze | Thaw and Final Filling portfolios. He earned his master's degree in science (biotechnology) at "Polytech Marseille" in Marseille, France.

As of 2014, he has been focusing on freeze | thaw technologies in different marketing and product management roles. As a subject matter expert in that area, he is working on Sartorius' global freeze | thaw strategy and supporting Sartorius' customers in the biopharma industry to establish reliable and simple frozen BDS management.

**Katy McLaughlin**
PhD, Scientific Content Writer, Sartorius

Katy is part of the Marketing Communications team at Sartorius, where she supports the creation of a variety of written pieces, from published articles to web content.

Before joining Sartorius in 2021, Katy was employed as a Post-Doctoral Research Associate at the University of Edinburgh, where she also completed her doctoral studies. Here, she carried out research in genetics and cellular biology and began taking on writing projects, eventually entering into a career as a freelance writer for various biotech companies and agencies.

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