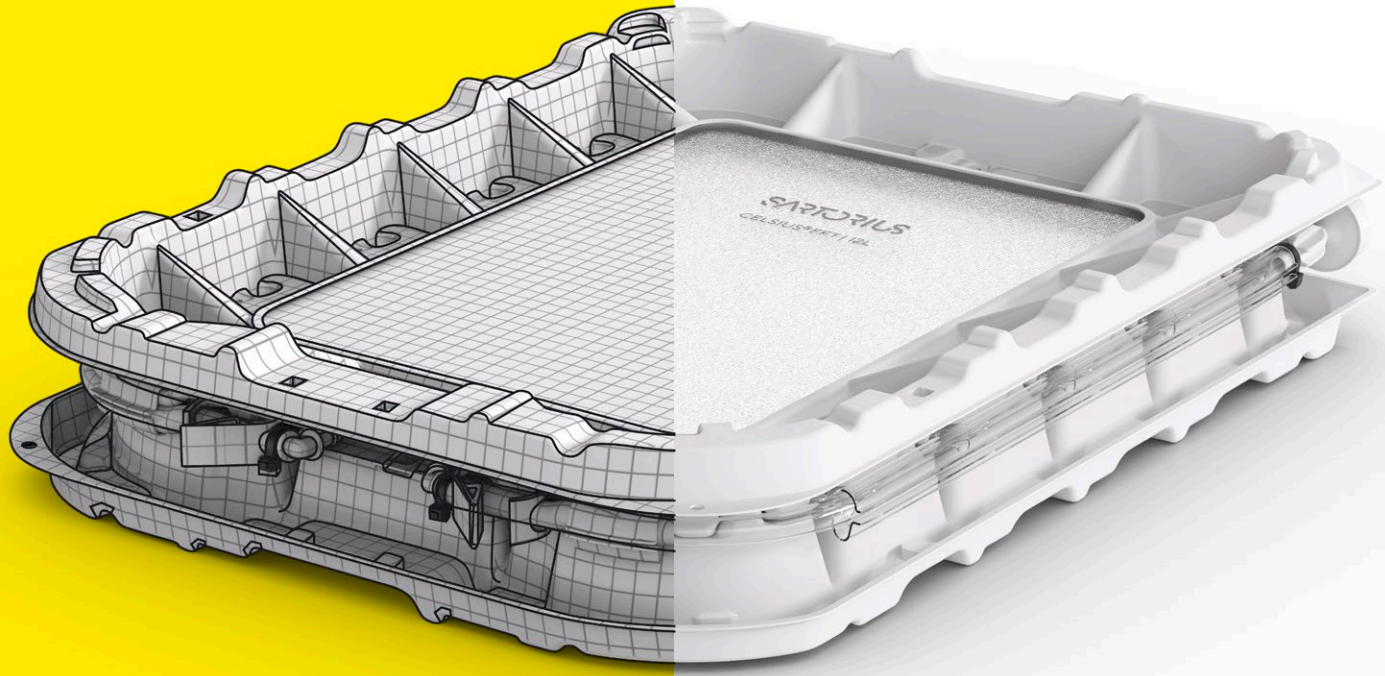

Simplifying Progress

Robust by Design: Addressing New Challenges in Bulk Drug Substance Management

December, 2022 | Marion Monstier, Katy McLaughlin

Keywords or phrases:
Freeze and thaw containers, frozen storage and shipment, Bulk Drug Substance, BDS Management, Cold Chain Management, Freeze & Thaw Platform

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Introduction

The biopharmaceutical industry is dynamic and increasingly global. Technologies, modalities, and regulatory standards continue to evolve, driving biomanufacturers to adapt their frozen storage and shipping solutions.

According to a report by Fusion Market Research, the pharmaceutical cold chain market is set to grow by USD 26.42 billion by 2030[1]. Over 95% of all approved biologics and 90% of all vaccines are cold chain dependent. However, up to 25% of vaccines are believed to be lost due to cold chain failures[2]. Modern cold chains should be supported by highly robust freezing solutions to meet new demands and help prevent losses.

+9.65% CAGR

Estimated Pharmaceutical Cold Chain Market Growth 2022–2030

This trend has been further confirmed by the new Annex 1 from the EU GMP which highlights freezing and thawing operations as critical steps, hence requiring appropriate systems to manage and reduce risks.

In this whitepaper, we discuss how a philosophy of "robust by design" and strong collaboration with industry players allowed us to develop the next generation of Celsius® FFT and FFTp containers.

Single-Use Solutions in Cold Chain Management

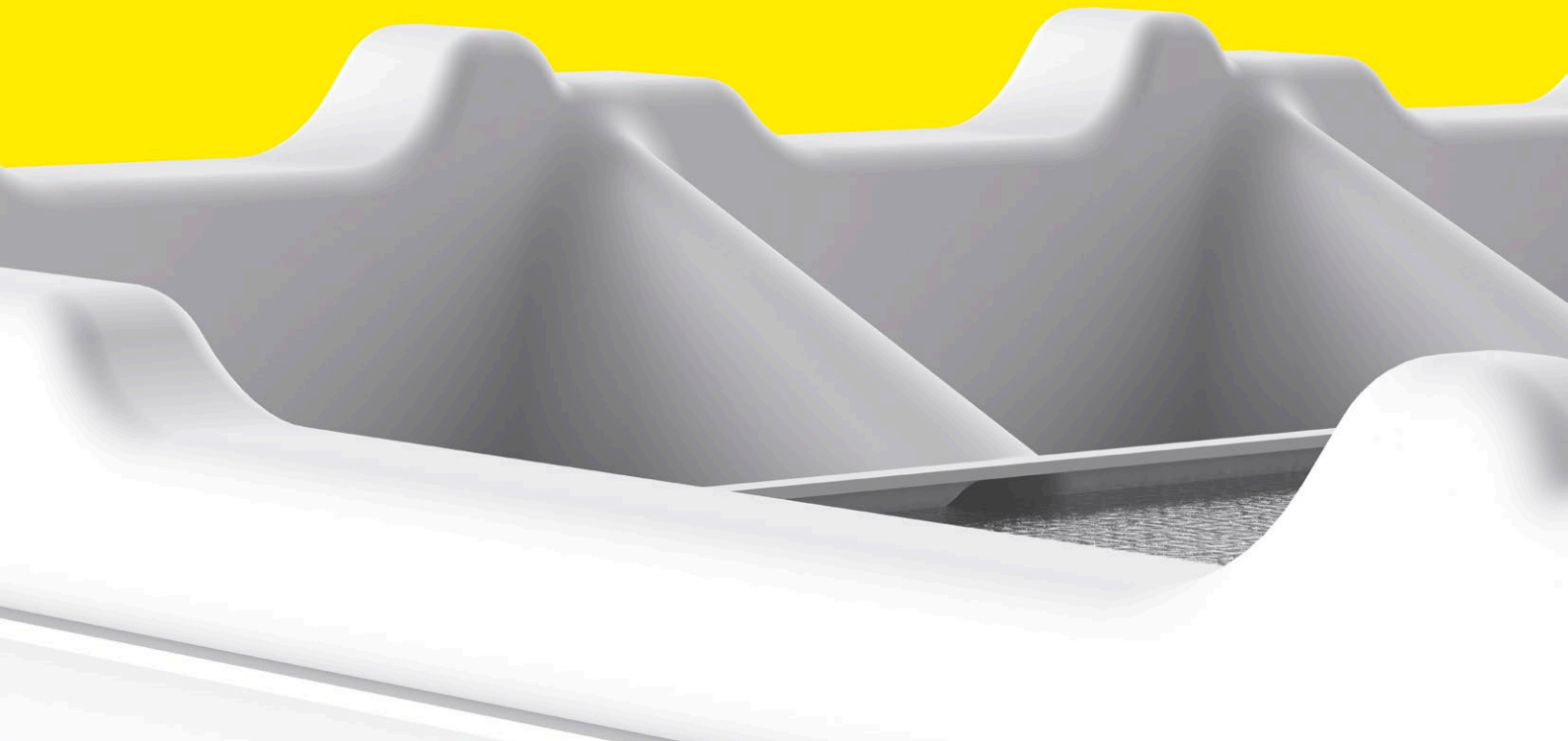
During storage and shipping, the integrity of the freezing container is the first line of defense against cold chain failures. The primary goals when designing a freezing concept is to avoid any leakage, product degradation, or contamination.

In line with the rest of the industry, biopharmaceutical cold chain solutions are moving increasingly towards single-use containers, which have various advantages over traditional bottles, including:

- Improved Consistency
- Aseptic Processing
- Greater Flexibility
- Fewer Handling Errors
- Reduced Footprint

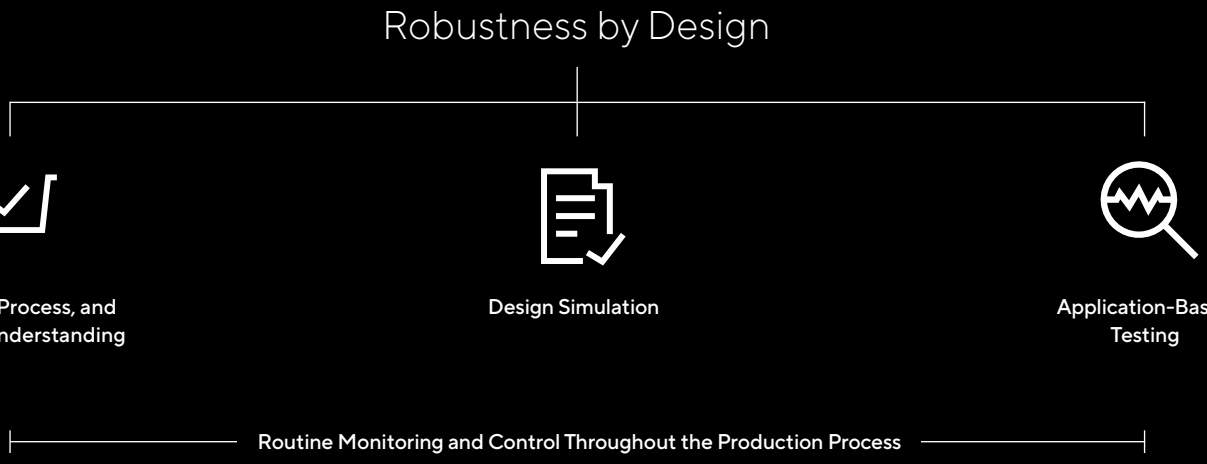
To offer these advantages, freezing containers require careful design, including adapted materials and protective packaging of sensitive areas. Single-use solutions, in particular, must be robust enough to resist being compromised by freezing, frozen handling, shipment, and thawing. Demonstrating these capabilities requires confirmation studies, which biomanufacturers might have limited resources to perform.

To overcome this challenge, biopharmaceutical companies would benefit from "robust by design" freezing containers based on characterization knowledge, design experience, and an understanding of real-world freezing applications.



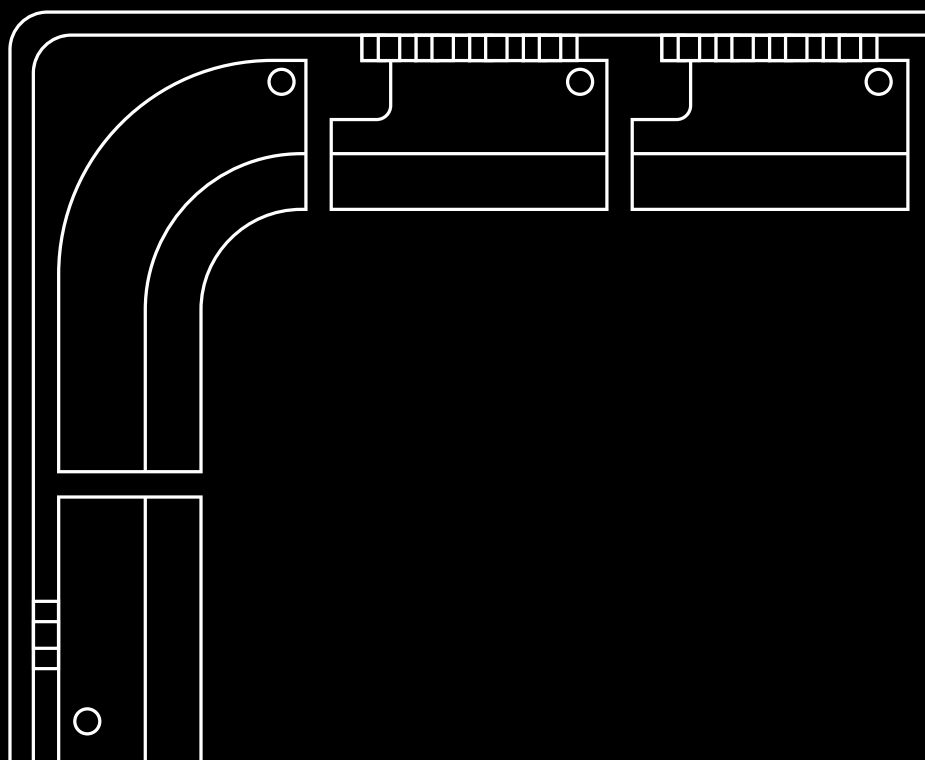
Three Pillars of Robustness by Design

The concept of robust by design is based on the principles of quality by design (QbD), a systematic, risk-based approach for process or product development. QbD starts with a defined target profile and places emphasis on the following:



Ultimately, a QbD approach aims to build quality into the product from the beginning and avoid reliance on increased testing to guarantee quality. A quality risk management approach incorporating QbD, validation tests, and routine controls maximizes robustness.

Developing a high-performing freezing container requires optimization across three core concepts: choosing suitable materials, designing the solution based on application-based simulations, and subsequently testing under real-life environmental conditions.

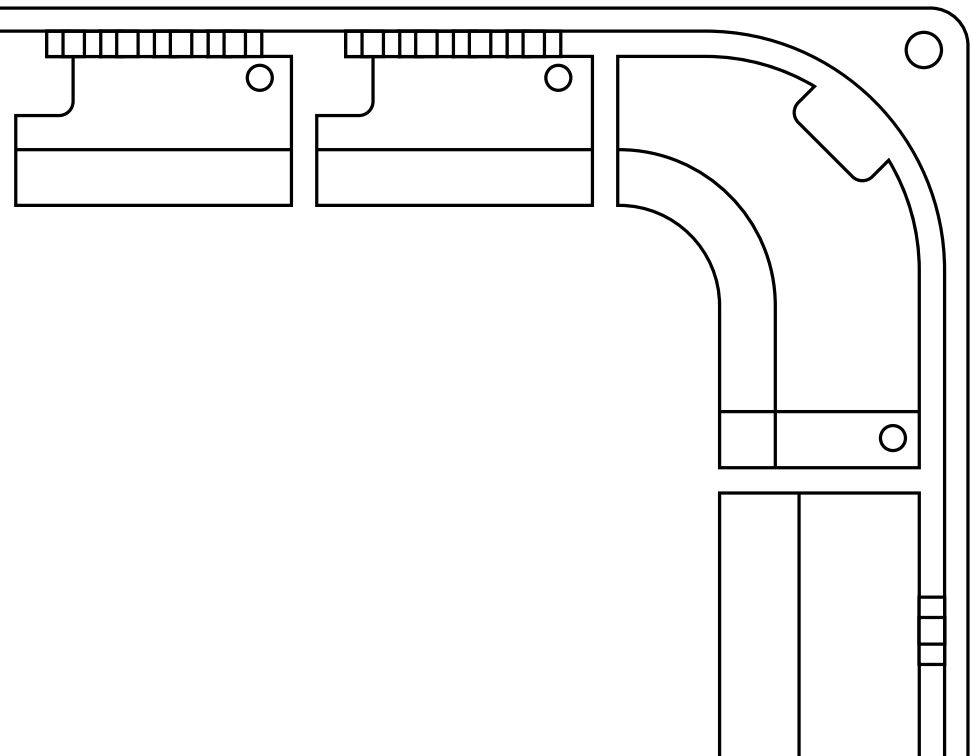


Material, Process, and Product Understanding

Material expertise is the foundation of QbD and is essential for robust freezing container development. This expertise relies upon the proper characterization of candidate materials at low temperatures to inform resource selection and container design during early development. Using diverse mechanical testing techniques and analytics provides a deeper understanding of how properties change with temperature, shocks, and impacts.

During the development of the second generation of Celsius® FFT | FFTp containers, Sartorius scientists performed dynamic mechanical analysis (DMA) to study the behavior of polymers at low temperatures and understand the changes happening at micro and macro scales. Mechanical characterization tests were also performed to determine material resistance at frozen temperatures and under conditions where stresses and impacts are common, such as during handling or shipping. Important parameters include tensile strength, impact resistance, burst resistance, and cold crack testing.

This comprehensive understanding of how material properties influence the real-life performance of the container is essential to the QbD concept.



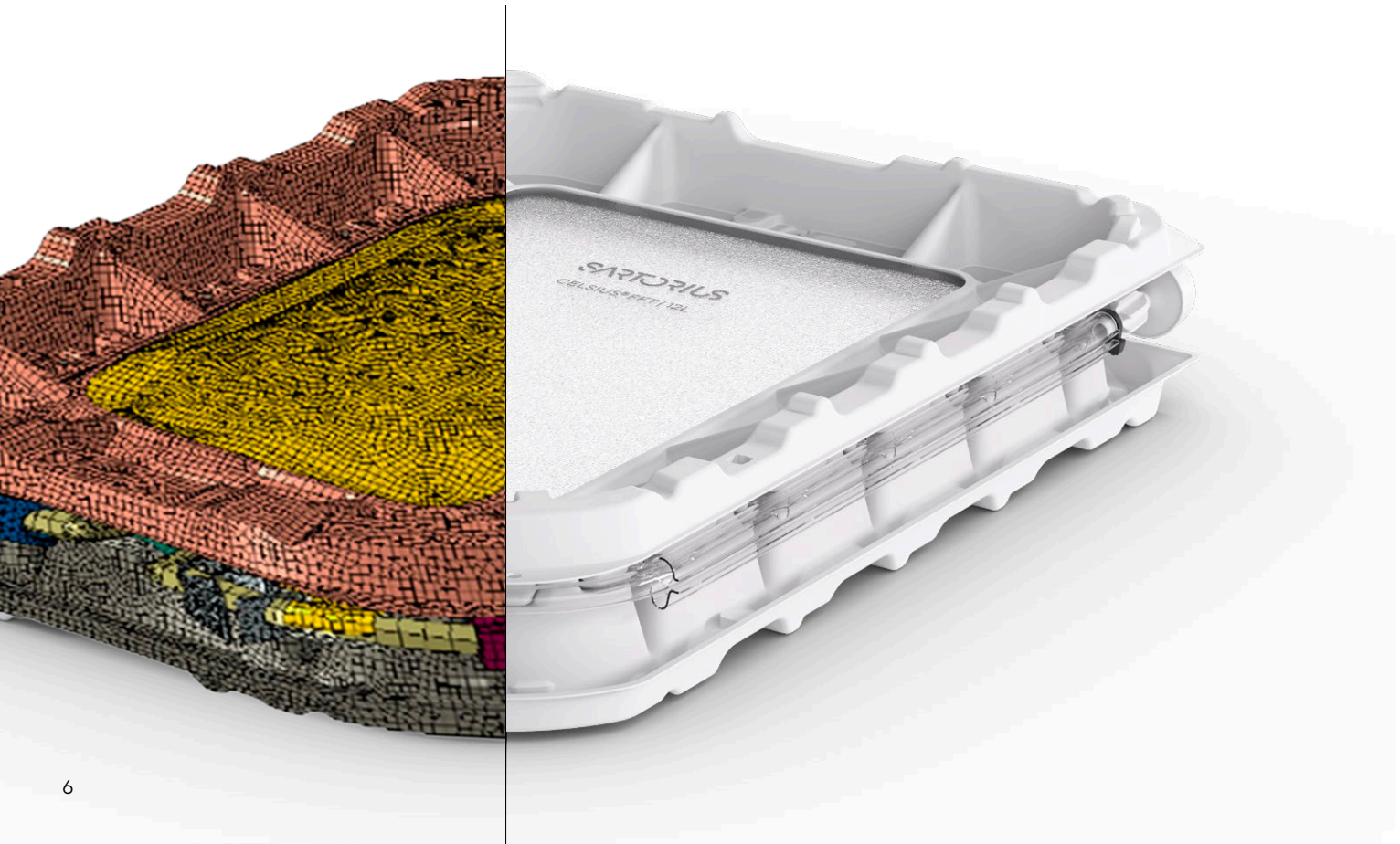
Design Simulation

Design simulations provide opportunities to adapt the container design to achieve the minimum level of stress to the identified most sensitive areas. Finite element analysis (FEA) is a design simulation tool used by Sartorius scientists and engineers to model the mechanical stresses applied to different parts of the container assembly during handling, freezing, and thawing.

FEA helped Sartorius engineers understand the behavior of Celsius® FFT | FFTp containers during their entire lifecycle. Simulations include, for example, container freezing, filling to maximum volume, and accidental drops. The most sensitive locations were mapped and observed in detail during multiple simulation runs to select the design that provided the reduced stress levels to the most sensitive areas, identified as bag ports, film welds, and tubing.

This FEA data allowed our engineers to quickly adapt the container design according to the simulation runs without lengthy real-life design iteration cycles and informed the "cassette" design of the Celsius ® FFT | FFTp bags, which includes insulation and cushioning. The entire solution was designed with a pre-assembled, sterile concept to avoid manual handling and assembly, a potential source of integrity failures.

Next, relevant application testing must be performed to ensure the design meets real-life requirements.



Application-Based Testing

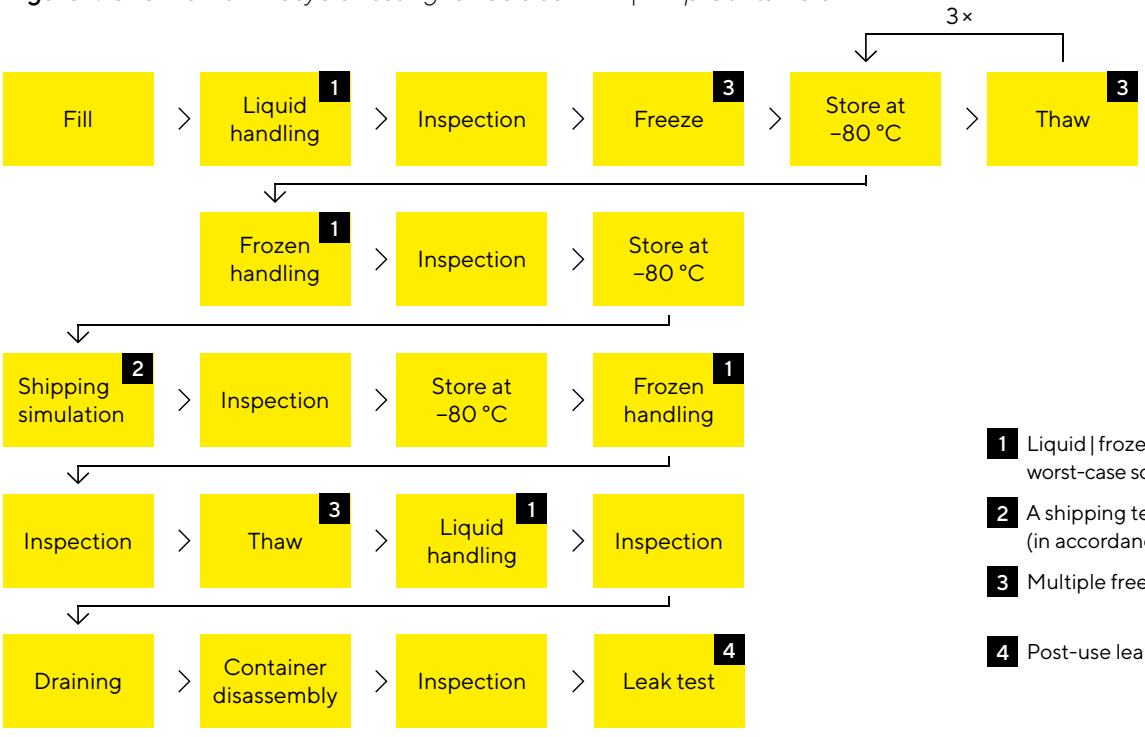
Demonstrating robustness requires deep application knowledge and an understanding of the product lifecycle in actual conditions of use. This knowledge comes from our 15+ years of experience with the first generation of Celsius® containers, fruitful end-user collaborations, and a complete understanding of standard and variant product life cycles.

By leveraging data collected from the material characterization and design simulations, Sartorius engineers were able to identify (1) the components and areas requiring further protection and (2) the best materials to offer that protection. The film and tubing were identified as the materials most sensitive to low temperatures. Therefore, the overall protection packaging was improved to immobilize these components and reduce potential stresses.

In order to properly test the final design, a comprehensive understanding of the applications of the freezing containers, including worst-case real-life stresses, is required, and a rigorous testing protocol and tools must be defined accordingly. The container should then be tested under true environmental conditions, including subjecting it to shocks, vibrations, and the temperature ranges it is likely to encounter during its lifecycle.

To perform this application testing, Sartorius engineers first carried out an ergonomic study, subjecting the freezing containers to all the steps of a typical workflow at drug substance and drug product sites. Several variables were tested, including different operator profiles, container volumes, heights, manipulation speeds, and frozen and liquid states. This information was used to design the final lifecycle study (Figure 1).

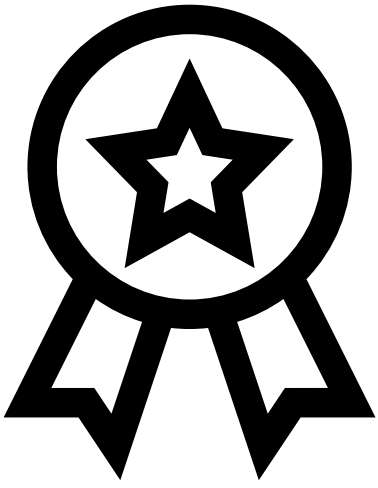
Figure 1: *Overview of Lifecycle Testing for Celsius® FFT | FFTp Containers*



Routine Monitoring and Control Underpin the Three Pillars of Robustness by Design

Establishing an effective control approach across the development and manufacturing process is essential to the success of any QbD strategy. Continuous monitoring of process performance and product quality ensures that QbD principles are maintained, and that mandatory compliances are met. Therefore, we continue to support confidence in the robustness of our Celsius® FFT | FFTp containers - provided by our initial expertise and validation studies – using routine in-process controls.

These in-process controls include visual inspections, bag leak tests, and determining product conformity to technical drawings. As freezing bags are used in critical applications and are in direct contact with drug substances | drug products, we apply further measures to control the system's integrity by applying supplier integrity testing (SIT). SIT is based on the detection of helium as a gas tracer and - with a detection limit of 2 µm - is correlated to microbial ingress. This final integrity test confirms the single-use system's robustness before shipping to the end user's facility. As a result, the containers arrive with a very high integrity assurance level, supplementing their intrinsic robustness guaranteed by their design (tailor-made for the application) and their extensive qualification according to their life cycle. This test is available on standard designs for all bag volumes and can also be evaluated for compatibility with customized designs.



Conclusion

A reliable cold chain requires container robustness at frozen temperatures and across all steps of the product lifecycle, including in-process handling, storage, and shipping. Specifically designed single-use freezing solutions offer many advantages over traditional stainless steel containers, plastic bottles, and carboys, including ease of use, improved aseptic processing, increased flexibility, improved sustainability, and enhanced reproducibility. However, the relatively recent implementation of single-use storage solutions across the biopharmaceutical industry means that more comprehensive performance validation studies are required.

More importantly for critical applications such as freezing of high value products, when not properly designed and tested, single-use solutions may not be robust enough to endure the handling conditions across the lifecycle. This introduces potential weaknesses in the cold chain that can lead to product losses. As such, validations must demonstrate the reliability of the single-use container across the entire cold chain operation.

Sartorius addressed key industry challenges in the development of the second generation of Celsius® FFT | FFTp containers, which are built on purpose-driven design to reduce manual handling of drug substances and minimize risks associated with cryo-concentration and frozen transport.

The assurance of single-use freezing container integrity was demonstrated by an initial robustness validation and is continuously verified by routine process controls. As a result, these freezing containers have robustness built into their entire lifecycle via QbD principles and extensive validation work. Key features, including superior protection offered by the 'bag in plates' system, are summarized in Figure 2.

Figure 2: *Key Features of the Second Generation of Celsius® FFT | FFTp Containers*

This development approach, centered around "robust by design," allows drug developers to leverage the suppliers' validation work to alleviate their in-house workload and limit the risk of process failures.

Discover more about how we develop and demonstrate robustness.
Ask us for the full Robustness Qualification Report.

For more information on freeze management, visit
www.sartorius.com/en/products/fluid-management/frozen-storage-shipping/commercial-scale-solutions

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Marion is currently a Product Manager in charge of the Celsius® FFT and FFTp product range. She joined Sartorius in 2016 as a field application specialist for fluid management technologies where she was involved in many industrial projects for design, implementation and validation of single-use systems. Marion then moved to product management, first focusing on fill and finish technologies before transitioning to freeze and thaw technologies in 2021.

Marion earned her master's degree at the Biotechnology Engineering Institute of Bordeaux in France.

Katy McLaughlin
PhD, Scientific Content Writer,
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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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Status: 11 | 2022