SINGLE USE SUPPORT.



CASE STUDY

The hidden cost of ambient thawing

How controlled plate-based ADC thawing in single-use bags protects product value while improving manufacturing flexibility and operational readiness.

SITUATION

Frozen storage preserves drug substances until they are required for further processing. During thawing, however, validated temperature and hold-time limits become increasingly relevant, requiring the material to be returned to a processable state under controlled conditions and with minimal thermal exposure.

A global manufacturer processing high-value antibody-drug conjugate (ADC) drug substance used single-use bags larger than 10 L for these cold chain operations. The bags were removed from ultra-low temperature storage and thawed under ambient conditions. A 10 L bag required approximately 16 hours before the material was available for further processing.

LIMITED PROCESS CONTROL DURING AMBIENT THAWING

Although this approach required no dedicated thawing equipment, the process depended on room conditions, bag position, fill volume, and operator assessment. This limited reproducibility and required production planning around an extended waiting period.

In addition, prolonged thawing extended the period during which the material was no longer maintained in a frozen state but had not yet progressed to the next controlled manufacturing step. This extended exposure period introduced additional operational and product-related risks. The long thawing duration also reduced the time available for filtration, formulation, filling, or transport within the validated post-thaw window.

Thawing requires controlled heat transfer through the container and the already-thawed liquid until the frozen core has fully transitioned to the liquid state. At the same time, the material must remain below its defined temperature limit. Non-uniform thawing can also result in concentration gradients and cryoconcentrated regions that persist until the product is fully thawed and homogenized. As shown in Fig.1, inhomogeneity of the product may require additional mixing, sampling, review activities, or process investigations before manufacturing can proceed. [1]

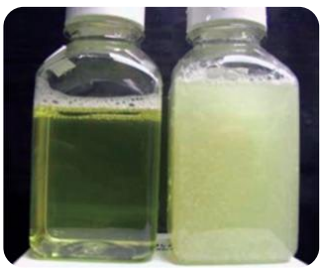


Figure 1: Illustrated damaged protein structures after controlled thawing with faster freezing rates (left bottle) are preferable for reducing non-homogeneous aggregated proteins with uncontrolled freezing-thawing (r.) [2]

SOLUTION

The ambient process was replaced by a recipe-driven procedure with defined temperature profiles and documented process parameters.

1

The manufacturer implemented **Single Use Support's RoSS.pFTU** as a controlled thawing platform for large 2D single-use bags. The plate-based freeze-thaw system was selected because it is well-suited to 2D single-use bags as primary packaging. In contrast, RoSS.BLST blast freeze-thaw system provides greater process flexibility for bottles or other container formats.

2

The single-use bag is protected by **Single Use Support's RoSS® Shell**, as it provides the rigid, standardized geometry required for plate-based freeze-thaw processing and protects all available single-use bags during handling in the frozen state. Direct contact between the plates and the protected bag geometry supports efficient heat transfer across the product surface.



The objective was to establish a reproducible and scalable GMP-compatible manufacturing process, rather than simply reducing thawing time alone. Standardized thaw profiles and protected bag handling were intended to reduce process variability, preserve the available post-thaw processing window, support product homogeneity, and improve manufacturing planning.

RESULTS

The controlled process reduced thawing time from approximately 16 hours to 5 to 6 hours per 10 L bag.

Thanks to this time saving, material could be prepared closer to the point of use, reducing the additional scheduling allowances previously required for downstream operations. Across 50 thawing operations per year, the reduction corresponded to approximately 500 hours of thawing-related waiting time removed from the annual production schedule. However, speed alone was not the primary benefit: Process control enabled greater manufacturing flexibility, improved operational readiness and enhanced product protection.

Controlled thawing and protected bag handling also reduced product exposure to temperatures above the defined process target. According to the manufacturer's internal assessment, handling-related product loss exposure decreased from approximately 0.5% with ambient thawing to 0.1% with the controlled process.

The manufacturer claimed that approximately 10% of thawing operations under the previous ambient thawing process required additional review, investigation, or corrective processing related to product homogeneity, cryoconcentration, or other quality observations. Standardization of the thawing profile largely eliminated these interventions, reducing the burden on quality control (QC), quality assurance (QA), and manufacturing science and technology (MSAT).

THAWING TIME	ANNUAL WAITING TIME	PRODUCT LOSS EXPOSURE
16 h to 5-6 h	**~500 h removed**	**0.5 % to 0.1 %**

HOW TO REDUCE PRODUCT LOSS DURING THAWING

Product loss during thawing can result from ADC instability, cryoconcentration, product inhomogeneity, and exposure to off-target temperatures.

Controlled thawing helps minimize temperature deviations and supports more uniform thawing conditions, reducing the risk of product loss.

ROI ANALYSIS

The manufacturer assessed the financial impact based on a 100 L antibody-drug conjugate batch with a product value of approximately €10 million per thawing operation. The site-specific total cost of ownership (TCO) calculation assumed approximately 50 thawing operations annually.

The largest contribution to the projected return on investment resulted from the product value protection. Reducing the assumed handling-related product loss exposure from 0.5% to 0.1% corresponded to approximately **€2,000,000 in product value saved annually**.

This value reflects product value protection only and does not include:

- Avoided mixing, sampling, quality review, and investigation activities, which represented an additional operating benefit in the TCO model.
- The approximately 500 hours removed from the annual thawing schedule were not regarded as direct labor savings. Their operational value resulted from improved manufacturing readiness, reduced scheduling allowances, and greater flexibility in coordinating subsequent process steps.



Based on the combined impact, the manufacturer projected that the investment in controlled thawing equipment would achieve **pay back within one year**.

CONCLUSION

For high-value biologics, the impact of thawing extends far beyond the duration of the process itself. Replacing passive ambient thawing with a controlled process preserved more of the available post-thaw processing window, reduced product exposure, minimized quality-related interventions, and improved manufacturing readiness.

While the ROI analysis indicated a payback period of less than one year, the value of controlled thawing extended beyond cost savings alone.

Improved process consistency, greater manufacturing flexibility, enhanced product protection, and increased operational readiness were equally important outcomes for the manufacturer.

As a result, the business case for controlled thawing was driven not only by product value protection, but also by the ability to establish a more predictable, scalable, realiable, and GMP-compatible manufacturing process.

References

[1] Minatovicz B. et al: Large-Scale Freeze-Thaw of Protein Solutions: Study of the Relative Contributions of Freeze-Concentration and Ice Surface Area on Stability of Lactate Dehydrogenase. 2023. Journal of Pharmaceutical Sciences, Volume 112, Issue 2, February 2023, Pages 482-491

[2] Bezavada A, et al.: Use of Blast Freezers in Vaccine Manufacturing. 2011.

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