

Single-Use Systems for Storing and Shipping Frozen Drug Materials – Every Component Counts



PROCESS FLEXIBILITY WITH EXTENDED REACH AND COST SAVINGS

Freezing in single-use assemblies allows pharmaceutical manufacturers to expand their reach, increase their process flexibility and efficiency, reduce their capital requirement, lower their operating costs by enabling batch processing, and ultimately serve more patients in a shorter time.

Pre-sterilized single-use systems require no cleaning or sterilization. Maintenance and validation times are reduced. Large volumes of an expensive biological drug substance can be frozen in batches to allow the drug product to be manufactured based on real-time commercial or clinical demands.

It has become common to geographically decouple global drug substance bioprocessing from final drug product manufacturing: Large amounts of the drug substance can be produced at one site, and then the material is frozen into many smaller units and shipped to different sites for final drug processing. Use of integrated, single-use freeze-thaw systems composed of plastic bio-containers, bags, tubing, and connectors is now standard for the industry.

Although the biological drug material used in cell and gene therapies is technically not a drug substance, it requires the same seamless transportation between sites. Freezing the biological material in single-use assemblies has been the enabling technology for managing the logistics. Autologous cell therapies use the patient's own cells collected in a hospital or clinic, then sent to a lab to be manipulated, concentrated and then returned to the clinic to be injected into the patient as therapy. Because the patient's cells are the active

pharmaceutical ingredient. There is less margin for error for container failures and logistic errors. Time is of the essence, and there may be very little material reserved as a backup. All the components of the single-use freeze-thaw system are part of the solution to improve the health of a sick patient.

DRUG SUBSTANCE INTEGRITY VIA FREEZING AND SINGLE-USE SYSTEMS

Regulations mandate biopharmaceutical product quality be controlled throughout manufacturing, storage, transportation, and delivery to patients. Operations often include freezing and thawing of a bulk drug substance, dilution of that purified substance to a target concentration, filtration, filling into a selected container-closure system, additional processing, inspection, packaging, storage, transport, and delivery. Biologics, large molecule drugs, are particularly susceptible to degradation. Freezing is commonly used to overcome the dilemma. It allows biological integrity of a drug substance to be maintained while an array of logistics can be implemented. And, it can safeguard product quality while waiting for precious downstream processes.

Freezing is better than liquid storage for long-term storage and shipping of the drug substance. The freeze-thaw application can also be expanded to process intermediates as a means of extending hold times between steps. It is easier to maintain temperature-control requirements in a frozen state, and there are fewer interactions between the bulk drug and the container. In addition to reducing product degradation, it mitigates risks associated with mechanical stresses that come from relocating containers from

room to room of a manufacturing facility, or country to country within an international manufacturing network.

As biopharmaceutical companies move into new markets and launch new clinical research programs, including drugs involved in gene, cell, and tissue therapies, the cold chain resembles that of bioprocessing and its integrity is more important and challenging than ever.

Using pre-sterilized, single-use freeze-thaw systems instead of traditional freeze-thaw methods that utilize stainless steel tanks and bottles helps manage the quality of the drug substance. Single-use assemblies reduce the risk of cross-contamination and the complexity of dispensing and manual interventions during freezing, thawing, handling, and shipping. Single-use assemblies can be designed with a shorter freeze-path length, the distance from the edge of a container to its center: This allows more uniform heat transfer between different areas within the total volume of drug material and leads to a more homogeneous mix of biological components and a more stable product. Single-use bags can be conveniently stored in freezers of different styles and dimensions.

EFFECTIVE IMPLEMENTATION

Successfully implementing the freeze-thaw process requires careful testing of the physical and thermal properties of the single-use system, as well as the integrity and quality of the drug substance. Frozen drug substances are usually stored at temperatures ranging from -20°C to -80°C for transportation or in-process holds, and more and more drug manufacturers are moving to the lower part of the range for improved results.

The mechanical properties of single-use assemblies are complex. Attention needs to be paid to the materials

used to construct the individual components — the bag, tubing, and connectors, as well as the design and configuration of the system, together with any shell or frame used for support. The assembly needs to be tested under expected and exaggerated conditions used for freezing and thawing, to simulate normal and possible unintended conditions such as mechanical or vibrational stress or temperature excursions. If multiple freeze-thaw cycles are anticipated, testing of that parameter must be included.

Peace of mind can be achieved by selecting proven and robust single-use solutions from trusted suppliers. Although the biopharmaceutical company or its contract research organization must do a complete validation of the drug substance in the single-use system used for freezing, they can streamline the process by first understanding their supplier's test parameters and results for the components and single-use assemblies they use. Best results are achieved through a collaborative effort between the scientists and engineers from the supplier and end user organizations: material scientists, process and manufacturing engineers, specialists in film extrusion and plastic molding, quality and validation personnel, and product and system design engineers.

It takes a well-designed system to ensure a frozen drug substance retains its integrity. Problems that arise from poor implementation come with a significant cost. With single-use systems, plastic material tends to become brittle at low temperatures and must be carefully selected and protected from mechanical stresses caused by handling and shipping. In addition to the single-use container holding the drug substance, the design of the protective shell, tubing and connectors, and secondary packaging must be considered to preserve the precious drug material throughout its

journey and life cycle.

CPC ADVANTAGE

CPC focuses their expertise on innovative fluid connection technology important to the single-use assemblies used in the freeze-thaw process. To ensure the assembly functions without failure during storage, transportation, and manipulations before and after, CPC has perfected its seal designs and offers connectors with tested robustness that are also easy to use. CPC's connectors are tested for their intended use, as well as unattended abuse. They have followed the motto "simple is better" in the design of their connectors to explicitly reduce the risk of operator error.

CPC's aseptic connectors marry well with the sterile plastic containment bags (Figure 1) needed for freeze-thaw processing. The connectors allow the end user to make a sterile or aseptic connection in uncontrolled and controlled environments (Figure 2). Each connector half has a protective barrier, usually a membrane, which prevents bacteria and contaminants from entering the fluid pathway while the barrier is in place and opens a sterile fluid pathway once the two components of the connector have been brought together (Figure 3). Bacterial ingress testing is used to demonstrate the ability of the aseptic connectors to make and maintain a sterile connection during use under extreme conditions.

Freezing single-use assemblies puts added stress on connectors. CPC tests its connectors against mechanical stress under freezing and thawing operations within the temperature range of -20° C to -80° C now requested by biopharmaceutical end users. The seal design is tested to make sure it functions as it should and withstands mechanical side-loading, flexing, and tensile forces without compromising the integrity of the seal after the freeze thaw process.

Testing and validation of all raw materials that are used for CPC's connectors is ensured. Extractable testing of the connectors is complete, reliable, and relevant to the downstream needs of the end users. CPC offers genderless connectors, in which the two components that are brought together are identical, thereby eliminating inventory-planning and design issues associated with gendered connectors and simplifying the design of a single-use system.

Overall, the adoption of a well-tested, robust, simple-to-operate, single-use connection technology drives a standardized approach to future components and platform designs. Reduced system complexity and production costs are important to biopharmaceutical companies. Decoupling drug substance manufacturing from final drug product formulation and logistically moving biological material for cell and gene therapies are two new paradigms that are only conceivable because of single use tools that have recently been developed. Single-use assemblies with reliable component parts, such as the connectors supplied by CPC, are paving the way to new possibilities.



Figure 1.
Sterile Plastic Containment Bag for Freeze-Thaw Processing.¹



Figure 2.
AseptiQuik G Connectors.

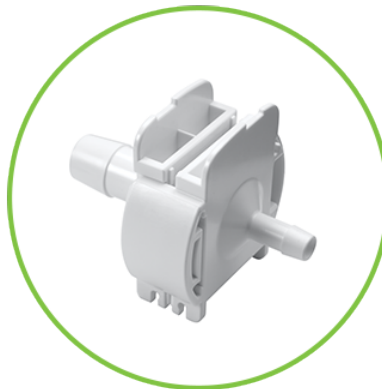


Figure 3.
AseptiQuik Connector Body with Protective Barrier.



About CPC

CPC (Colder Products Company), the leader in single-use connection technology, offers a wide variety of bioprocessing connection solutions. Our innovative designs offer flexibility to easily combine multiple components and systems including process containers, tubing manifolds, transfer lines, bioreactors and other bioprocess equipment. AseptiQuik® Connectors provide quick and easy sterile connections even in non-sterile environments—a critical capability for biopharmaceutical and bioprocessing manufacturers. Featuring a wide range of options including 1/8- to 1-1/2-inch sizes and genderless and gendered connections, AseptiQuik connection technology delivers sterile, high-quality single-use connections and easy media transfer with less error risk. For additional information visit cpcworldwide.com or call +1-800-444-2474.

REFERENCES

1. GORE, GORE® STA-PURE Flexible Freeze Container and designs are trademarks of W. L. Gore & Associates. Image used with permission.

Confidence at every point of connection.

