Entegris

Cold-chain Bioprocessing Readiness:

Mitigating Risk and Protecting Pharmaceutical Products

White paper

INTRODUCTION

The pharmaceutical industry is migrating rapidly toward a world where drugs, vaccines, and specialized therapies are available on demand to patients anywhere around the globe. Whether accelerating clinical trials to bring new drugs to market or developing biosimilars to give more patients access to established commercial drugs, small and midsize production facilities stand to benefit from growing demand. To do so, however, they must be prepared to handle a broader mix of products and increase throughput without sacrificing safety or reliability, while at the same time keeping life-saving medications affordable. Such challenges become more difficult when working with products that must be stored and shipped in a frozen state.

Many pharmaceuticals — monoclonal antibodies, vaccines, and patient-specific therapeutics — must be reliably stored and transported at sub-zero temperatures, requiring a robust cold chain that continues throughout downstream processing (Figure 1). Demand for these pharmaceutical products is on the order of hundreds of kilograms per year and continues to increase.[1] While large manufacturers are already well-equipped to handle these volumes, it is possible for smaller laboratories to quickly adapt to produce a wide variety of specialized drugs and distribute them without compromising safety or increasing financial risk.

Proper implementation of single-use technology is the key to success. Laboratories that are scaling up pharmaceutical manufacturing will benefit from a thorough understanding of the best way to process, store, and ship products using pre-sterilized, modular components and systems. Some companies are new to single-use packaging for bioprocessing and are unfamiliar with the available options for single-use bags and assemblies, but even those that already implement single-use plastic packaging should re-evaluate their needs as their product mix changes and new single-use products are introduced to the market.

Manufacturers that are expanding the range of products they process often find themselves working with cells that are more sensitive to temperature exposure. For laboratories accustomed to working at room temperature or under basic refrigeration conditions, adjusting to frozen product storage requires a shift. The colder the storage temperature, the closer manufacturers need to look at their single-use component library. At these colder temperatures, there is a greater likelihood that components that may have previously worked — bags, tubing, or connectors — will fail.

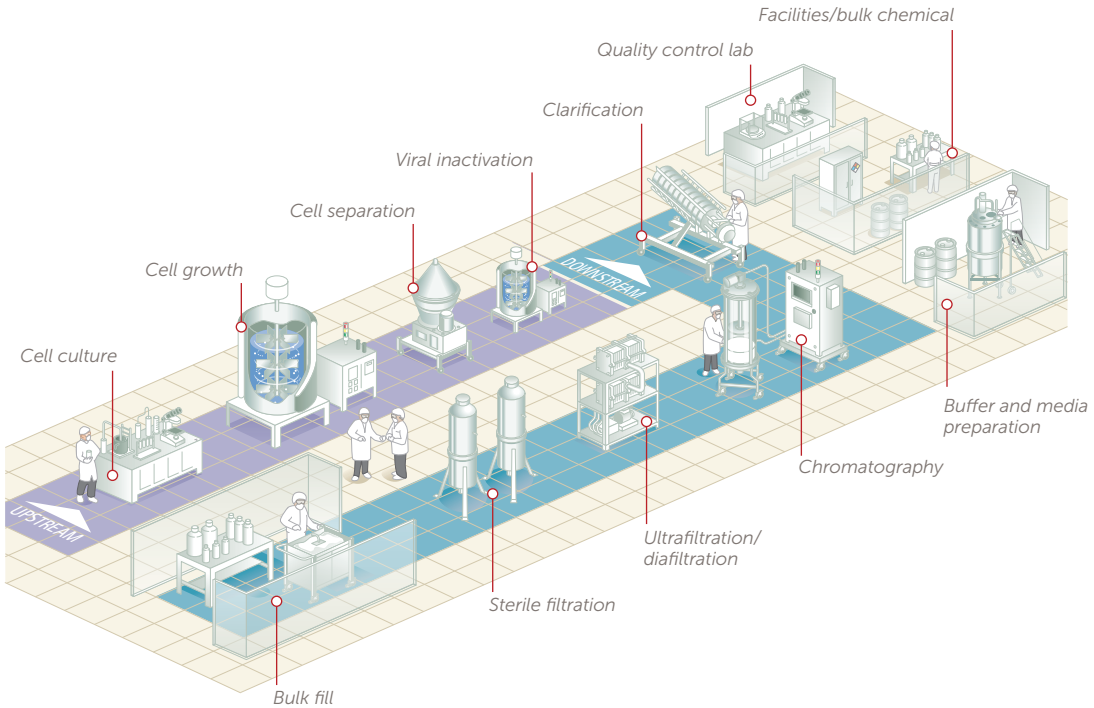

Figure 1. Overview of cold chain. Source: Entegris

Companies that are increasing production volumes or developing new partnerships may now need to ship products between different facilities using cold storage and shipment. They may need to send products over longer distances to reach processing facilities and patients around the world. Shipping adds risk, and the high value of the pharmaceutical products being shipped makes failure more expensive. Single-use systems that may have previously worked within one facility may no longer be the best choice. Protecting high-value pharmaceuticals needs to remain the highest priority.

This white paper addresses the concerns of development laboratories, contract manufacturing organizations (CMOs), and contract research organizations (CROs) and explains several factors they should consider when expanding operations and selecting single-use systems for cold-chain bioprocessing.

PROTECTING PRODUCT QUALITY

Product quality is critical for biopharmaceuticals, and those that must be kept frozen need packaging that can withstand extreme temperatures and rapid temperature changes without suffering mechanical damage. Independent of temperature exposure, storage systems for bulk drug products cannot introduce unwanted contaminants. Customers must be confident that a pharmaceutical product meets all safety and efficacy requirements.

While some pharmaceuticals can remain at relatively high temperatures hovering near the freezing point of water, others must be stored at temperatures as low as -85°C, requiring dry ice for shipping. For certain products, even -85°C is too warm. Drugs for cell and gene therapy applications typically require temperatures between -85° and -196°C (cryogenic conditions). At -196°C, the temperature of liquid nitrogen, many polymers that perform well in less demanding conditions become brittle and susceptible to fracture during handling or when undergoing multiple freezing and thawing cycles.

For development labs, CMOs, and CROs, ensuring that single-use packaging can withstand all steps of processing, storing, and shipping, reduces the risk for their pharmaceutical customers and increases customer satisfaction. Choosing the optimum materials and configuration goes a long way in improving outcomes and avoiding costly failures.

Proper selection and thorough auditing of suppliers will:

- Minimize the risk of mechanical damage that can cause product loss
- Avoid extractables and leachables (E&L) that can contaminate the product
- Accommodate multiple freezing and thawing cycles at various temperatures
- Allow high-value drugs to survive shipping and long-term frozen storage
- Allow rapid scale-up without increased cost
- Ensure that biopharmaceuticals can pass required FDA and ISO safety and quality standards

MITIGATING RISK OF PRODUCT LOSS

Product loss during processing, shipping, and storing pharmaceuticals occurs for two primary reasons: (1) physical breakage of bags, tubing, or connectors, or (2) contamination of the drug. Optimum single-use packaging materials and configurations can mitigate both causes of failure. Manufacturers should only buy components from suppliers that provide documentation that demonstrates proper adherence to performance, quality, and regulatory requirements. Doing so is one step in creating a reliable supply chain, but it is not sufficient to ensure a successful outcome.

When storing and shipping pharmaceuticals, components that functioned flawlessly at relatively mild temperatures may fail when temperatures approach their lower operating limit. Multilayer polymer bags, which had long been the only option available for single-use bioprocessing, are not usually rated below -70 °C. They contain polymers that are not intended for cryogenic use and the multilayer construction contributes to unacceptable cold temperature performance. The glass transition temperature and coefficient of thermal expansion differ for the various layers, causing interlayer stresses that can in turn lead to delamination between the layers if the bag is frozen or thawed quickly. A 2015 industry survey showed that many pharmaceutical manufacturers were concerned about bag breakage as well as leaching of contaminants from the adhesives used to tie together the various bag layers.[2]

As discussed in the paper, *Advantages of Single-layer Film vs. Multilayer Film for Use in Bioprocessing Bags*, single-layer fluoropolymer bags (Figure 2) provide an alternative to multilayer films.[3] Fluoropolymers remain flexible at extremely cold temperatures and are typically tested or rated down to -196°C. Bags made from these materials have successfully passed drop testing at temperatures ranging from +2° to -85°C with no damage when filled with frozen liquids, and strips of the fluoropolymer material passed cold crack bend testing down to -188°C (the lower limits of the testing machine).[4]

Figure 2. Single-layer bag made from fluoropolymer material with attached tubing and connectors. Source: Entegris

Controlling E&L is critical for drug quality, and the risks are related not only to bag construction but with how the bag materials interact with the product inside. Potential sources of E&L include adhesives, catalysts, and a variety of polymer additives including plasticizers, stabilizers, and pigments. The release of chemical components from polymers can vary depending on the pH and polarity of solvents used in drug manufacturing, so characterization of bag materials must account for expected exposure and usage conditions, including sterilization methods. Manufacturers should request test results from potential suppliers. Suppliers that follow the Bio-Phorum Operations Group (BPOG) E&L protocol are implementing best practices around testing and risk assessment.

The single-layer construction of fluoropolymer bags eliminates the need for adhesive tie layers and the accompanying delamination and E&L risks associated with these adhesives and multiple layers. Fluoropolymers are chemically inert and are considered "polymers of low concern." They have extremely low levels of E&L regardless of exposure to different solvents and environmental conditions.[5]

Whether considering multilayer or single-layer polymer films, development labs, CMOs, and CROs should make sure that the bags they are buying have been tested and proven to be suitable for their process, application, and conditions. Buying validated components and systems for process needs will mitigate the risk of potential failures or defects, while also reducing the cost of extensive in-house quality testing.

Relevant parameters include not only storage temperature and shipping time but compatibility with the pharmaceutical ingredients and the desired sterilization process. Gamma irradiation, the gold standard sterilization method for the industry, damages many conventional fluoropolymers. Ethylene oxide or autoclave sterilization are an option, but most customers prefer — or even require — gamma irradiation. Bags made from certified gamma-stable fluoropolymers are now commercially available, giving manufacturers a way to satisfy both freezing, E&L needs, and sterilization requirements.

SINGLE-USE BAG AND SHELL CONFIGURATIONS

Single-use bags are available in either a flat (2-D) pillow style or a 3-D cylindrical or rectangular shape. The 2-D bags are preferred for storing relatively small volumes of bulk pharmaceutical products, typically up to a maximum of 50 liters. These bags are also ideal for products that require sub-zero temperatures because they offer a greater surface-to-volume ratio than 3-D bags. While 3-D types allow for much larger volumes they have more freeze/thaw associated risks, 2-D bags can be thawed more rapidly, thereby minimizing possible adverse effects on product quality during thawing. Lastly, 2-D bags can accommodate the addition or removal of the product without introducing air into the bag.

Rapid freezing and thawing, however, increases the risk of mechanical damage. Expansion during freezing induces mechanical stress that can cause fractures in bags, tubing, or connectors. To reduce the chance of breaking or leakage, bags should not be overfilled beyond the maximum recommended volume.

Beyond selecting an appropriate bag material, development labs, CMOs, and CROs must also select a protective shell to mitigate the risk of damage during frozen storage and shipping. The shell provides mechanical isolation, protecting the bag assembly from vibration-induced damage. Two types of shells are available: plastic and metal.

Stainless steel (SS) shells incorporate top and bottom SS plates for optimum heat transfer and the fastest, most uniform freezing and thawing profile. Protective foam inside the shell isolates the bag and attached components from damage resulting from handling or accidental dropping (Figure 3).

Rigid plastic shells made from polycarbonate or high-density polyethylene (HDPE) are a lower cost option for mechanical protection. The plastic shells include an inner film that cushions the bag, creating an air gap between the bag and the shell. While plastic shells assist with heat transfer, they do not do so as rapidly as SS shells.

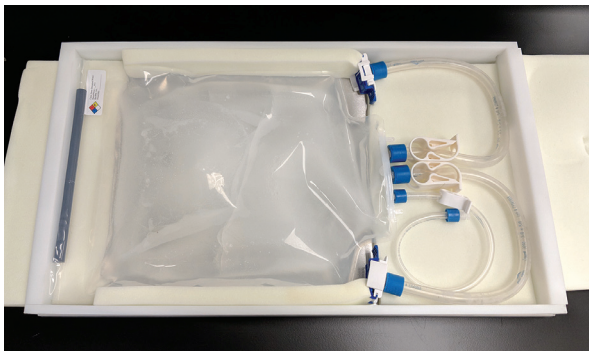

Figure 3. Fluoropolymer bag filled with liquid and loaded into a stainless-steel shell. To further protect the valuable product, an additional layer of foam will be placed over the tubing and connectors before closing the shell with the top plate. Source: Entegris

It is important to consider the product mix and production volume when selecting protective shells. Some shells come as a system, where the bag and shell are sold as a unit. This option ensures compatibility between the bag and shell and is convenient but does not allow for maximum flexibility regarding bag material. Shells sold independently from bags can be either adjusted or custom-designed to fit a variety of bag configurations — including placing multiple bags within one shell if desired for efficient use of freezer space — and are compatible with both multilayer and single-layer bags.

By sourcing fluoropolymer bags and SS or plastic shells separately, users remain agile and able to quickly change setup based on demand for product volume and temperature requirements. They can consider stocking an optimum mix of single-use packaging to meet changing demands while balancing freeze and thaw time, ease of handling, and transportation needs.

ADJUSTING FOR PRODUCT MIX AND VOLUME

Single-use bags come in a wide range of sizes to accommodate production requirements. Increases in production volume, however, do not necessarily merit an accompanying increase in bag size. Several smaller bags may be a better choice than one large bag for shipping a given quantity of product even if a large enough bag is available. Multiple smaller bags take more time to process and increase packaging costs, but filling and handling are easier, and the associated processing and storage equipment is more compact and less expensive.

Regardless of the cost of packaging materials, the safe keeping of the drugs far exceeds the value of the storage options. For high-value pharmaceuticals, suppliers often decide that the potential economic loss from damage to a large bag poses too great a risk. When a bag as small as five liters can contain $500,000 worth of product, the potential losses are considerable. Manufacturers can save millions of dollars per year by choosing single-use materials that can survive the entire cold chain process.

Development labs, CMOs, and CROs wanting to accommodate a wide range of products will ideally provide packaging materials that can withstand any anticipated temperature exposure. If they streamline their bag assembly options, they can quickly adapt to process any drug without needing to qualify and keep an inventory of multiple types of bags. Given the trend toward drugs that require cryogenic storage, choosing materials that can function in the widest temperature ranges is wise.

SUMMARY

Single-use systems allow small and midsize development labs, CMOs, and CROs to scale up quickly as they expand their bioprocessing production to a wider range of pharmaceuticals and a broader geographical area. Drugs requiring extremely cold storage in the range of -85° to -196°C demand additional care, and equipment breakage or product contamination cannot be tolerated. When selecting suppliers for single-use bags and associated equipment, manufacturers should consider the following:

- What is the temperature rating?
- Has the supplier provided test data to demonstrate the equipment's ability to withstand cold chain processing, storage, and shipping?
- Has the equipment been certified for compatibility with gamma irradiation or other desired sterilization methods?
- Has the equipment passed US Pharmacopeia (USP) standards for factors such as biological reactivity, particulates, endotoxins, and physiochemical containment?
- Is the equipment available in the sizes and quantities needed?
- Does the supplier provide a complete solution (bags, tubing, connectors, and protective shells) or are compatible components readily available?

Failure in any part of a single-use system can result in market opportunity losses and unacceptable risk to patient health, timely drug development, product yields, and total costs. By carefully selecting bag assembly components and working with suppliers that adhere to industry-leading practices, development labs, CROs, and CMOs can assure their pharmaceutical customers that high-value drugs will be processed, stored, and shipped safely and reliably while maintaining product quality, purity, and efficacy.

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