Entegris

Employing Single-use Technology to Control Frozen Bulk Drug Storage:

The Cold Hard Facts

White paper

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Biogen

In collaboration with Biogen, Inc. and Single Use Support GmbH

OVERVIEW

New biopharmaceutical drug products that alter and even save lives can be very profitable for their developers. They are, however, costly to develop and represent significant investment, particularly at the end of the manufacturing process. For this reason, safe cost-effective frozen storage and transport are critical, especially as drugs transition from R&D through clinical trial and to higher volume production. The objectives for choosing a new storage/transport method include minimizing both capital and operating expense, reducing facility space requirements, and cutting time and energy for clean-in-place and steam-in-place processes. At the same time, valuable product must be protected from cross-batch or other sources of contamination.

The traditional approaches for primary packaging in frozen applications have been bottles and stainless steel cryo vessels. While each has its strengths, both have significant shortcomings. Bottles are bulky, non-scalable, and can slow freezing and thawing. A system of cryo vessels is costly to build and operate and adds layers of complexity in the return, cleaning, and reuse of vessels. For these reasons, manufacturers are adopting a system of single-use bags to eliminate bulk, scale as necessary, control freezing and thawing, and eliminate the need to manage container returns and reuse.

Single-use technologies have been increasingly adopted over the last 15 years to help solve critical process challenges and to robustly manufacture across an international landscape, (Figure 1).[1] The advantages of implementing single-use technologies have been well documented and include among others improving manufacturing consistency across multiple sites, reducing footprint in cleanroom facilities, improving process economics/plant flexibility, and reducing clean-in-place (CIP) and steam in place (SIP) operations.

The adoption of single-use bags has challenges of its own that must be overcome to fully realize the benefits of the technology. It must have the ability to accurately scale up from low-volume production in the sub-10 L range to phase three clinical pilot and full-scale manufacturing that will exceed 300 L per batch. The materials of construction must be able to withstand the very low temperatures at which frozen drug substances are stored (-80°C or less) and must also maintain integrity through both freezing and thawing processes.

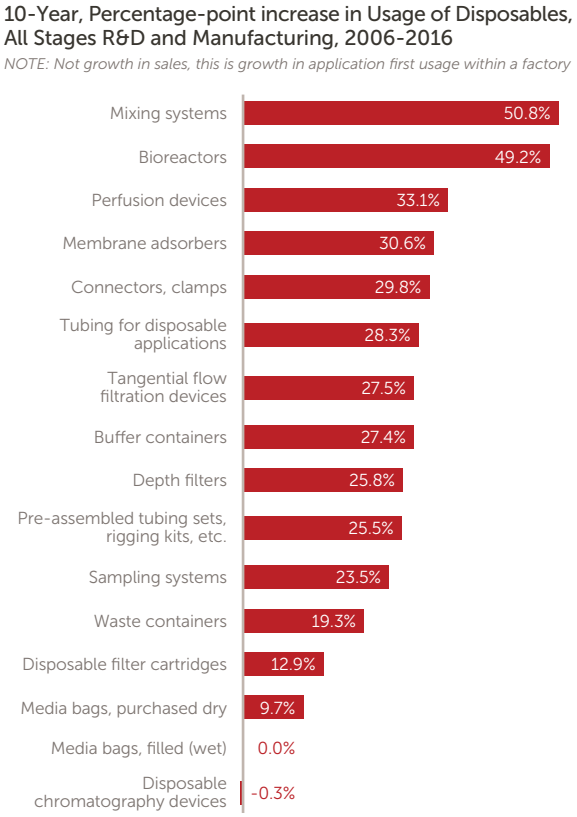

Figure 1. 10-year percentage-point change in first-usage of disposables, 2006-2016.[1]

Depending on the manufacturer's risk tolerance and the drug's stage of development, single-use bags will ideally be used for storage volumes as small as a few liters or as large as hundreds of liters, so scalability is important. A complete freeze/thaw system can optimize protection, safe handling, storage, and transport mechanisms of bagged materials.

This paper addresses the challenges of bulk drug substance (BDS) storage, shipping, and other critical factors users must consider in deciding whether and how they will adopt the technology. It will touch on material challenges and on the filling, freezing, storing, transporting, and thawing process requirements that single-use packaging must meet. Finally, it will present specific options to consider in moving toward single-use drug substance storage.

COLD HARD FACT: MANUFACTURERS ARE SLOW TO ADOPT SINGLE-USE TECHNOLOGY FOR BULK DRUG SUBSTANCE

Single-use technology has found its way into many upstream and downstream processes of drug development and manufacturing. It appears in bioreactors of all sizes, in cell amplification and separation systems, and in disposable filtration and chromatography systems, (Figure 2). There are plenty of product and system options in most of these operations and product performance has been well characterized.

Unfortunately, BDS, the final step in the manufacturing process, is behind in adopting single-use technology. Due to regulation, the life impacting nature of drugs, and their monetary value (especially in larger volumes), manufacturers are understandably cautious about adopting new technologies in sensitive operations. Besides being familiar, existing technologies – bottles and cryo vessels – each have their strengths. Bottles are relatively inexpensive, and stainless steel cryo vessels are robust and can easily accommodate large volumes of a drug substance. To be widely adopted, single-use systems will have to meet a number of criteria and demonstrate proven benefits that equal or exceed those of the existing methods.

COLD HARD FACT: BULK DRUG SUBSTANCE PROCESSES VARY

Any change in storage methodology has its challenges. It will entail capital expenditure, and the cost of switching will have to be justified by significant benefits from the new methodology. A primary process-related challenge is the high degree of drug substance process variability within the pharmaceutical industry, which will likely continue for the foreseeable future.

One contributing factor is the process life-cycle. More specifically, what stage of development any given product is in. For example, it is common for early stage clinical products to produce small volumes of drug substance. The use of single-use drug substance bulk freeze containers in the 5 – 20 L volume range have historically been the norm. However, while this size offers an acceptable operational fit for dispensing drug substance for smaller volume pharmaceutical manufacturing processes, it is not ideal for larger volume dispensing process. It is typical for commercial programs to generate several hundred liters of drug substance per batch. If it can be safely done, filling fewer large containers is simpler both in operation and in system design. A larger number of small containers requires more elaborate filling and dispensing manifolds and connections and more complex handling throughout the process.

On the surface, the obvious choice may be to create larger volume containers. However, effectively freezing large volumes of drug substance in a single, large storage container can be problematic. For example, freeze rates of Active Pharmaceutical Ingredients (API) can vary. Drug substance (API) concentration differences as well as product-specific formulation buffer matrices (excipients, cryo-preservatives, etc.) can also result in variable freeze/thaw rates, even for products with similar volumes. Generally, larger volumes take longer to freeze, which can adversely impact API stability by forming product ice bridges, migration, and stratification. Therefore, users of large volume drug substance bulk freeze containers must consider freeze/thaw rates as well as dispense, handling, and storage functionalities.

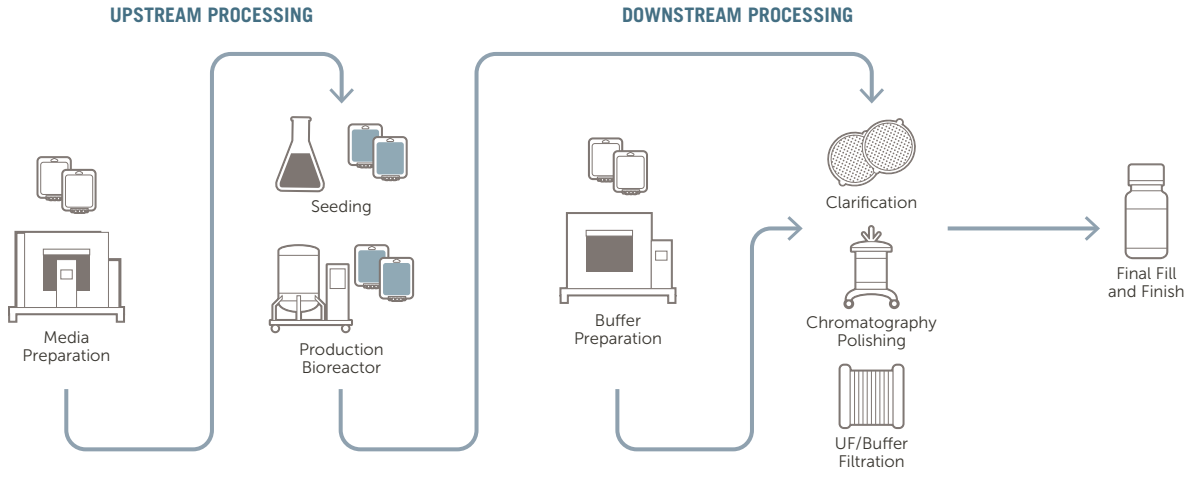

Figure 2. Single-use technology can address a diverse set of challenges in upstream and downstream bioprocessing. Source: Entegris

In terms of risk mitigation, there is a perceived tradeoff in the pharmaceutical industry regarding the size of drug substance bulk freeze containers. On one hand, larger volume containers offer more simplified options for both drug substance filling and for final compounding, drug product filling operations. On the other hand, failure or contamination of a small container incurs far less cost than that of a large container. For these reasons, manufacturers may want to choose among a range of vessel sizes and configurations.

COLD HARD FACT: SINGLE-USE MATERIALS MUST ADVANCE FOR USE IN BIOPHARMACEUTICAL MANUFACTURING

Single-use technology itself is not new and is well established in several fields. Bags have long been used successfully for packaging food and other consumer goods and are used in the medical field for storing saline, blood, and other liquids. During its initial adoption of single-use technology, the bioprocessing industry relied on these existing polymeric materials to satisfy its need for disposable containers. For an industry built on a platform of stainless steel, this initial foray into plastics was met with great anticipation, yet there were many lessons to be learned.

Commodity films were cheap, plentiful, and well characterized. However, the bioprocessing industry learned that the critical temperature, chemical compatibility, and cleanliness requirements of drug manufacturing could not be satisfied using the same polymeric films used to produce products such as blood bags, construction supplies, grocery bags, and protective wrap.

As with all technology, material advancements have been made. Polymer selection has become more focused and suppliers are continually improving their polymeric expertise. Even so, there are several performance requirements for bulk drug substance storage that only recently have been addressed through the development of advanced polymers. To meet the needs of downstream processes, it is imperative that polymeric film maintains mechanical integrity at -80°C or below, has a low to non-existent extractable profile, and has a non-reactive gamma stable surface.

Breakage Risk at Cold Temperatures

One fundamental material property that can be used to determine if a polymeric film is suitable for use in cold temperatures is the materials glass transition temperature (Tg). This is the temperature range at which the material transitions from a pliable rubbery state to a hard relatively brittle and glass-like state, Figure 3.

Polymer Glass Transition

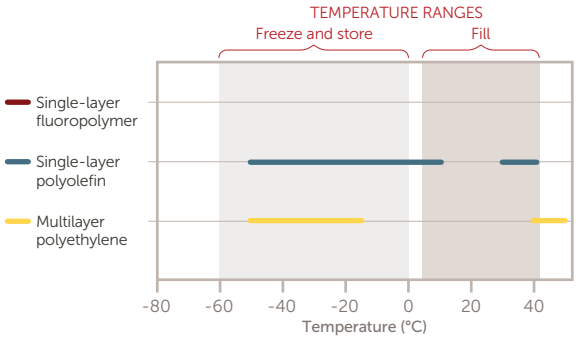

Figure 3. Within the transition range, materials are either gaining or losing mechanical strength depending on whether the temperature is increasing or decreasing. This is important in determining how a polymer film will behave in an application.
Source: Entegris

When looking at the Tg of polymeric films and the temperature range used to freeze, store, and transport bulk drug substance, polyolefin materials transition from a pliable material to a brittle glass-like state, so it is no surprise that bags using a polyolefin, such as polyethylene, fail. The Tg of fluoropolymers, on the other hand, is outside of this freezing range meaning the mechanical properties of the film will not change during the freeze/thaw cycle, resulting in an extremely robust container at cold temperatures. Choosing the right material for your operating conditions is vital to protecting the integrity of valuable BDS while it is exposed to extreme temperatures. (Figure 4).

Polymer Temperature Capabilities (°C)

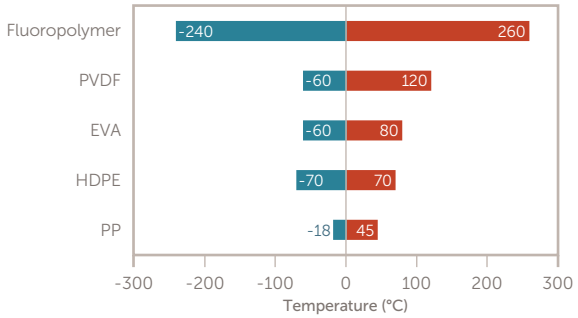

Figure 4. Fluoropolymers have a wide temperature operating range and their robustness at cold temperatures provides higher security of frozen drug product, improving process yield. Source: Compass Publications Chemical Resistance Guide for Plastics, ©2000

Contamination Risk from Chemical Leaching

Typical film materials that have been adopted for bioprocessing, while adequate for upstream applications, pose a risk to downstream. Given they are carrying high-value pharmaceuticals, in addition to being robust at low temperatures, single-use bag films must not leach contaminants from the process contact surfaces. Most packaging films consist of the base polymer and a variety of additives including antioxidants, plasticizers, cross-linking agents, and more. In the case of multilayer films, adhesives are used to bond the film layers together. These compounds and potential polymer degradation byproducts are typically the analytes that show up during an extractable or leachable study.

By eliminating additives in the resin formulation, fluoropolymers have proven to be the cleanest polymeric film on the market. Sourcing single-use bags made from advanced material fluoropolymers that will not leach or degrade helps mitigate the risk of contaminating valuable process fluids in downstream processes.

Non-reactive Gamma Stable Film

Gamma irradiation is the preferred sterilization method in biopharmaceutical manufacturing, however, it can be damaging to many polymers currently being used for single-use packaging. While they have similar mechanical properties and temperature range capabilities, not all fluoropolymers are suitable for exposure to gamma irradiation. When adopting advanced polymeric materials for drug substance storage, it is paramount to collaborate with a supplier that has materials science expertise and can recommend a gamma stable film that is the best material match for your drug substance storage needs.

COLD HARD FACT: SYSTEMS DEVELOPMENT CAN REQUIRE SIGNIFICANT CAPITAL

Choosing the optimal single-use bag system for freeze-and-thaw applications is the first step in transitioning to more efficient, cost-effective solutions for BDS processes. To facilitate the use of this single-use system in filling, freezing, storing, transporting, thawing, and draining processes, a series of decisions, often requiring significant capital, also need to be made. Finding solutions for each process step, establishing that the hardware and accessories work together, and ensuring the final setup will consistently produce the desired output are major decisions for any team.

Given the potentially large capital investment, it is important to look for suppliers with the knowledge and product solutions to support all BDS freeze and transport processes. This can be a difficult undertaking as most suppliers can address only a portion of the process, such as filling or transport, and may not provide a holistic solution that ensures their products interact with other equipment used throughout the process. And be careful of getting locked in with suppliers that provide expensive equipment that ultimately does not meet all process needs. Collaborating with a supplier that offers a full, end-to-end solution and is receptive to addressing all your process challenges is key to finding the right solution that will significantly improve process consistency and yield.

After having chosen the right bag and system for bulk drug substance, the evaluation can move onto bag handling and protection through the freeze-and-thaw process. Protective shells, or cassettes, are often used to mitigate the bag handling risks, (Figure 5). When evaluating protective shells for valuable downstream processes, there are many considerations: materials of construction, equipment compatibility, the effect on speed rates and consistency, to name a few. Asking the following questions may lead users toward more strategic decisions:

- What evidence is there for the protective shell's performance throughout the process?
- How do the shells impact freeze-and-thaw cycles?
- Are the shells compatible in existing freezing equipment?
- Do the shells significantly increase the storage space for each bag system?
- Are the shells able to scale with the product through process development?
- Do the shells increase supply chain complexity?

Figure 5. Asking the right questions when sourcing protective shells is key to reducing the risk in freeze/thaw operations. Source: Single Use Support GmbH

Finding the optimal shipper for frozen product is the next major decision when scaling up to clinical trial manufacturing. Readily available and with many options, shippers protect internal contents and keep frozen BDS temperatures when shipping across countries or continents.

Traditionally, protective shells are shipped in Styrofoam™ boxes packed with dry ice to maintain temperature. For lower-cost product, this process is adequate. However, for high-value products, it is critical to consider more sophisticated technology, such as temperature-controlled packaging that maintains temperature longer and ensures product integrity is preserved during shipment and protected from impacts, vibration, and potential delays.

When selecting temperature-controlled packaging consider the transport route, mode(s) of transport, and the anticipated ambient temperature profile over the duration of transport.[2] Thermal shippers can be configured to fit any process, whether it is a box for an individual bag or a crate for multiple bags in shells. And materials of construction can be designed to meet performance and price needs, with options including cardboard, corrugated plastic, or metal. Temperature of the drug substance is maintained in active systems using external power while passive systems use dry ice or phase change material (PCM) inserts.

BDS require a very controlled freeze-and-thaw process. Often bulk drugs can be adversely affected if freezing or thawing is too fast or too slow. Capital equipment for freeze-and-thaw operations can require a significant investment and is influenced by the complexity of the process and the expected production volumes. For simple freezing processes in small to moderate volumes blast freezers and even static freezers can do the job. For more controlled drug substance freezing, companies may want to turn to flat plate freezers or controlled rate freezers, which allow for better process control.

Thawing drug product has often been accomplished by simply placing frozen bags on tables to come to room temperature. If more control is needed over the thaw process, water baths have been used successfully. Flat plate freezers and controlled rate freezers provide additional options because they can both freeze and thaw, which reduces the amount of equipment needed for processing, saving valuable space.

SUMMARY

While single-use technology has been widely accepted in the field of medicine and in many areas of biopharmaceutical manufacturing, adoption for BDS packaging has lagged. This is largely due to difficulties in finding materials that do not leach chemicals into valuable drug product and can withstand the temperatures at which drugs are frozen. At the same time and largely because the materials had not been identified, scalable processes for packaging, freezing, storing, and handling single-use containers had not been developed.

The proven benefits of single-use packaging have driven research and development in BDS packaging, and suitable options are already being tested. Manufacturers can now seriously consider single-use bags as a viable and cost-effective option for bulk drug storage at every step of drug development and manufacturing. New systems can now package drugs at any scale, from a few liters during R&D to hundreds of liters during high-volume manufacturing. Innovative packaging materials are now available that will not contaminate sensitive biopharmaceuticals or become brittle at temperatures below -80°C. Additionally, multi-functional systems have been developed to quickly and safely freeze, thaw, store, and transport large-volume single-use bags.

The success of biopharmaceutical manufacturers relies on hitting performance targets at high yields. To reach these targets, new materials and process advancements can reduce both capital and operating expense, as well as the complexity of bulk drug packaging. Sourcing from suppliers with raw materials expertise and a solid understanding of the process requirements is paramount.

ABOUT ENTEGRIS

Entegris is a leader in specialty chemicals and advanced materials solutions for the microelectronics industry and other high-tech industries. Entegris is ISO 9001 certified and has manufacturing, customer service, and/or research facilities in the United States, China, France, Germany, Israel, Japan, Malaysia, Singapore, South Korea, and Taiwan. Additional information can be found at www.entegris.com

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ABOUT SINGLE USE SUPPORT GMBH

"Better support for the biopharma industry." Your single-use bag our ecosystem. We support single-use systems for biopharma and cell and gene manufacturing. SUSupport closes the gap between downstream and the fill & finish process in the biopharma industry. On the basis of single use bags, we offer biopharma companies access to a new and 100% secure logistics process for liquids. The technologies developed by us increase patient safety and minimize the risk of bio contamination and product loss towards 0%. Our mission is to increase patient safety by optimizing single-use technology in biopharma at the highest technical level.

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