



# Optimizing Bulk Drug Storage and Shipment: Key Considerations for Rigid Container Design



**BioProcess  
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SPECIAL REPORT



# Optimizing Bulk Drug Substance Storage and Shipment

## Key Considerations for Rigid Container Design

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Most discussions about single-use systems (SUS) for bulk drug substance (BDS) storage and shipment revolve around flexible systems (e.g., bags) that have been developed and commercialized over the past 20 years. However, rigid plastic containers such as bottles have been used for BDS storage for a much longer time and have a proven track record. That said, not all bottles have the same properties. Some bottles were designed for general laboratory use but have been repurposed for BDS storage. The associated risks to product quality and purity are significant.

Fluoropolymer containers — such as Savillex's Purillex bottles made from perfluoroalkoxy alkane (PFA), fluorinated ethylene propylene (FEP), and ethylene tetrafluoroethylene (ETFE) — are a recent addition to the SUS industry's assortment of rigid-plastic offerings. Purillex bottles are an excellent option for BDS storage, freezing, and shipment, not only because of the benefits offered by fluoropolymers, but also because the bottles were designed specifically for bioprocessing applications.

When considering BDS container robustness, whether for bottles or bags, users should focus on extractables and leachables, container-closure integrity, durability, gas permeability, and performance during freezing and thawing.

### EXTRACTABLES AND LEACHABLES

*Extractables* refers to organic and inorganic chemical compounds that are released from container systems in aggressive laboratory conditions (e.g., application of elevated temperatures and corrosive solvents). Under normal storage and use conditions, such compounds could migrate into a drug product as *leachables*. If extractable compounds are present, they must be examined for potential characterization as leachables based on their concentrations.

Fluoropolymers are the materials of choice for high-purity applications. They exhibit the highest purity levels among available materials for drug-



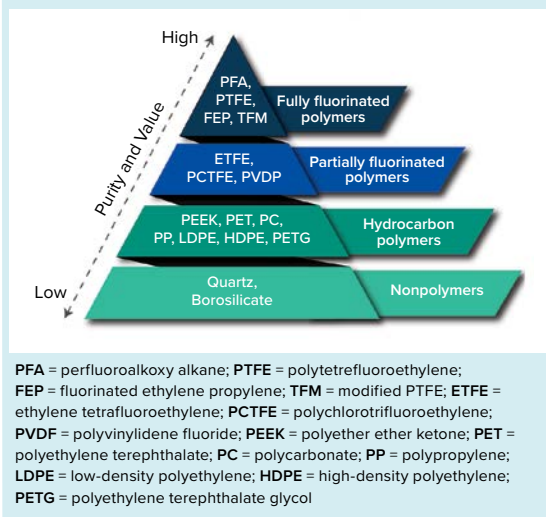
substance storage. Fluoropolymer vials made from PFA are used to store quality-control (QC) samples during extractables screening protocols and are called out specifically in several industry-standard procedures. Figure 1 compares the properties of commonly used bioprocess-container materials.

Results from multiple studies indicate that Purillex bottles release insignificant levels of organic and inorganic materials when exposed to solvents of different physicochemical properties under aggressive laboratory conditions. It also is well accepted that fluoropolymers generate the lowest extractable levels among materials available for drug-substance storage. Figure 2 provides a chemical compatibility comparison.

### CONTAINER-CLOSURE INTEGRITY

BDS storage and shipment require absolute container integrity to ensure sterility. Bottles are a natural choice for such applications because of their durable construction and strong closure systems. Closure-torque validation is key to rigid-container integrity. Standard laboratory bottles often are used for critical applications, but their closures can be made from different materials with distinct mechanical characteristics, and their seals are designed for general laboratory use. Inserted seals can fall out and become contaminated or even lost during use.

**Figure 1:** Fluoropolymers are inherently higher in purity and, because of their robust performance, higher in value than common hydrocarbon plastics.



The materials used in such closures and seals also present risks for high extractable levels.

Fluoropolymer bottles are an excellent choice because their superior closure designs ensure strong seals and thus robust protection of contents. Purillex bottle threads, lips, and closures are injection-molded to create precisely formed sealing surfaces. They also feature ferrule-style seals with no need for secondary seals or gaskets even in extreme conditions.

As specified in USP <1207> *Package Integrity Evaluation: Sterile Products*, container–closure integrity testing (CCIT) of bottle containers often involves helium mass spectrometry. Major biopharmaceutical companies have applied that technology and the ASTM F2391-05 (2016) *Standard Test Method for Measuring Package and Seal Integrity* using helium as the tracer (vacuum mode) to evaluate Purillex bottles. Such testing included application-specific validation of the bottles’ closure torque. Results (data not shown) indicated that the bottles’ helium leak rates fall within allowable limits (as determined by method feasibility studies), confirming the integrity of their closure package systems.

## DURABILITY

Most containers used to store BDS have glass-transition temperatures well above  $-85^{\circ}\text{C}$ . Many containers fail structurally during the rapid descent through glass transition. Even worse, such failures rarely are detected until after a container is thawed, which can be days if not weeks or months after freezing has occurred. Fluoropolymer materials, on the other hand, typically do not change structurally

**Figure 2:** Chemical compatibility comparison

		Chemicals					
		DMSO	Ethanol	HCl	NaOH	Tris buffer	
Materials	PFA	Compatible	Compatible	Compatible	Compatible	Compatible	
	FEP	Compatible	Compatible	Compatible	Compatible	Compatible	
	ETFE	Compatible	Compatible	Compatible	Compatible	Compatible	
	PETG	Incompatible	Incompatible	Semicompatible	Incompatible	Semicompatible	
	PC	Incompatible	Semicompatible	Incompatible	Incompatible	Incompatible	
	PP	Compatible	Compatible	Semicompatible	Compatible	Semicompatible	
	PE	Semicompatible	Semicompatible	Compatible	Compatible	Semicompatible	
	PS	Incompatible	Semicompatible	Semicompatible	Incompatible	Semicompatible	
			Compatible	Semicompatible	Incompatible		

when flash-frozen even down to  $-196^{\circ}\text{C}$ . Therefore, a container system manufactured from fluoropolymers not only can survive flash-freezing, but also will retain its room-temperature functionality.

Containers frozen to cryogenic temperatures are particularly susceptible to damage during handling. Because the containers become slippery, they also are easy to drop. Whether a container is dropped onto a surface from only a few inches or pushed off a counter (typically 3 ft or 1 m), damage can be catastrophic, leading to breach of bottle integrity and product loss. Again, such failures sometimes are detected only after thawing.

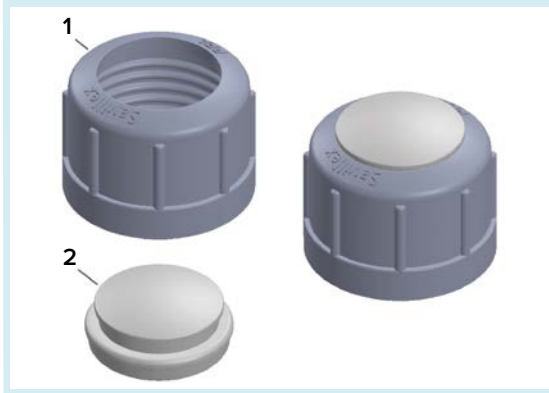
Evidence from our testing protocols demonstrates that Purillex bottles, even when frozen to  $-85^{\circ}\text{C}$ , can withstand a drop from 36 inches onto concrete with no damage and no loss of integrity. That result is a testament to the structural durability of fluoropolymer materials when exposed to cryogenic temperatures. It also emphasizes the strength, reliability, and seal integrity of Purillex bottles.

## GAS PERMEABILITY

Ingress of carbon dioxide into BDS containers during dry-ice storage and shipment is a serious and underappreciated problem. All bag systems experience that phenomenon to some degree because of thin wall construction and lack of CCIT. However, standard bottles also can have this problem.

Bottles are the containers of choice for freezing and shipping because they are durable, convenient, compatible with standard laboratory equipment, efficient for shelving and racking, and easy to transport in standard shipping containers. However, not all bottles undergo CCIT, and such testing provides no guarantee of leak-free performance once frozen. Carbon dioxide can enter bottles readily either through sidewall material or, more frequently, through closure-system leaks. Ensuring that closures

**Figure 3:** Two-piece closure design helps to ensure a consistent closure seal even down to liquid nitrogen temperatures.



are torqued to a validated specification is critical to maintaining container–closure integrity.

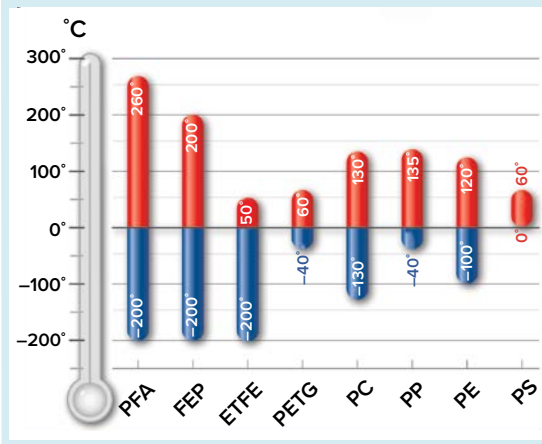
Fluoropolymer bottles work well for BDS processes because they do not change structurally when frozen. Therefore, most such containers maintain their seal reliability and sidewall integrity. The design of the closure system is key to ensuring reliable and consistent container–closure integrity. Savillex has designed a bottle closure with a novel snap-in insert. The two-piece insert design automatically centers and aligns the closure region to ensure consistent sealing, even down to liquid nitrogen temperatures (Figure 3).

During internal studies, bottles with the two-piece insert were filled with the lowest possible volume of formulation buffer solution and — as is done in approved commercial processes — frozen, then placed in a transport box and covered in dry ice. After a 14-day hold period, the bottles were tested to determine whether carbon dioxide ingress had lowered the solution pH. Test results indicate that the closure system effectively prevented measurable carbon dioxide ingress during the 14-day period.

### PERFORMANCE DURING FREEZING AND THAWING

Bioprocess solutions often are placed in frozen storage. Vessels used to store such materials must be capable not only of withstanding long-term storage in extremely cold temperatures (e.g.,  $-85^{\circ}\text{C}$  or  $-196^{\circ}\text{C}$ ), but also of maintaining their integrity after repeated thawing and refreezing. As with shipment processes, bottles are advantageous for freezing applications because they are durable, convenient, compatible with standard laboratory equipment, efficient for storage, and easy to transport. They also can undergo integrity testing during manufacture, often using a pressure-decay test method, and they feature container–closure systems that are ideal for torquing.

**Figure 4:** Bottle working temperature range ( $^{\circ}\text{C}$ )



One risk associated with standard laboratory bottles for freeze–thaw applications is *sidewall paneling*, or partial inward collapse of the bottle walls. Bottles panel for several reasons, with key factors including bottle material, sidewall thickness, and product design (e.g., cubical, round, or oval shape). More nefarious is that air egress can occur due to poor closure/seal design or inadequate closure application.

Fluoropolymer bottles are beneficial for freeze–thaw processes because they do not change structurally when flash-frozen. Results from freeze–thaw cycle studies conducted at Savillex indicate that Purillex bottles are suitable for multiple flash-freeze–thaw cycles down to  $-85^{\circ}\text{C}$  — and even flash-frozen down to  $-196^{\circ}\text{C}$  — with no observable material damage, leaks, paneling, headspace air egress, or loss of pressure integrity (Figure 4). The enhanced seal integrity of stretch-blow–molded bottles is a major factor in preventing leaks and bottle paneling during freeze–thaw cycles.

### THE PLACE TO START

When choosing a container for critical drug substances, the material of construction should be your first consideration. It is arguably the most important indicator of container success. Fluoropolymer containers such as Purillex bottles are an excellent choice for BDS storage, freezing, and shipment because of their proven physical and performance advantages. 🌐

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