

Savillex Technical Note

Freeze Drop Testing of Bulk Drug Substance Bottles

Summary

Frozen storage of bulk drug substance (BDS) at temperatures at or below -70°C is common in the life sciences industry. Storage below -80°C can lead to spontaneous failure of typical BDS containers, particularly if container temperature is reduced rapidly (also called flash freezing).

Most containers used to store BDS have glass transition temperatures well above -196°C ; many containers structurally fail during the rapid descent through glass transition. Even worse, these failures are rarely detected until after the container is thawed, which can be days if not weeks or months after the freezing is completed.

Conversely, fluoropolymer materials typically do not change structurally when flash frozen. Therefore, a container system manufactured from fluoropolymers has the potential to not only survive flash freezing but to also retain the same functionality it had when at room temperature.

Containers frozen to cryogenic temperatures are particularly susceptible to damage during handling. Because the containers become slippery, they are also easily dropped. Whether the container is dropped onto a surface from only a few inches or off a counter (typically 3 ft (1 m)), damage can be catastrophic, leading to breach of bottle integrity and product loss. Again, these failures are sometimes not detected until after thawing.

This technical note outlines a study performed to test the integrity of fluoropolymer BDS bottles after subjecting them to freezing down to cryogenic temperatures followed by a drop from 3 feet (1 m). Bottles were observed to ensure structural integrity after freezing and then dropped from a typical countertop height to see if bottle integrity was maintained. Finally, bottles were inspected post-thaw for any leaks or other structural damage that is undetectable when frozen.

Material and Cold Temperature Performance

Material of construction plays a crucial part in performance at cryogenic temperatures. For example, containers made from fluoropolymers like PFA and ETFE naturally perform better below -70°C . This is because fluoropolymers are innately more temperature stable and suitable for continuous use down to -200°C .

Another item to consider is the bottle closure system (i.e., the cap). Some bottles are manufactured using a different material of construction for the closure, sometimes even using closure inserts to ensure container integrity. This can be very problematic, as different materials behave differently at cryogenic temperatures. Also, bottles made from materials suitable for cold temperature applications could have closures made from materials that are not suitable for



Savillex Purillex ETFE and PFA 1 L Bottles

Savillex Technical Note

Freeze Drop Testing of Bulk Drug Substance Bottles

use at these temperatures. The container closure system of Purillex® fluoropolymer bottles has a superior design, which ensures a better seal and better protection of contents even under blast freeze conditions. The identical fluoropolymer resin type and grade are used for both bottle and closure, and both bottle thread and closure are injection molded, ensuring precise fit and superior seal integrity without the need for a closure insert. Thus, only a single material is in contact with the product.

Bottle Freeze Drop Test Procedure

Seven 1,000 mL (1 L) of each of the following bottles were selected for testing from the same bottle lots:

- Savillex Purillex PFA bottles
- Savillex ETFE bottles

All bottles were sterilized prior to testing. Each test bottle was filled with room temperature purified water to the minimum working volume of 1000 mL.

Bottle closures were tightened to 45 pounds-inch using a calibrated dial torque wrench. Each closure was brought to the proper torque and held at the value for 10 seconds.

All bottles were frozen to -85°C for a minimum of 24 hours prior to testing. This temperature was chosen as it is the lowest temperature setting of commercially available, upright freezers that do not use liquid nitrogen as a cooling source.

Drop Test Procedure

Bottles were selected in random order for drops. The bottles were dropped from a height of 36" (1 m) onto a hard, concrete surface. Bottles were dropped to impact on either the bottom or side, which are common impact orientations for bottles dropped while being moved around manually or from being knocked off lab countertops. It was also common for bottles to bounce and rotate after the initial impact, striking other surfaces during the drops.

Each bottle was inspected for damage immediately after the drop and again 24 hours later after completely thawed. The second inspection was performed since minor damage that cannot be detected on frozen bottles due to frost buildup on the bottle surface may occur. Bottles were also inspected for paneling after thawing. Paneling is the inward deformation of sidewalls caused by a slight vacuum that occurs in the bottle on thawing. This occurs if the closure leaks during freezing, allowing air to escape as bottle contents expand, but remains sealed during thawing. If the sidewalls are not strong enough, the small vacuum that is formed inside the bottle can cause the sidewalls to deform inwards.

Results

All bottles survived freezing to -85°C without any visible damage or structural failure. Therefore, all bottles moved on to the drop procedure. The results of the study are summarized in Table 1. All seven PFA and seven ETFE bottles survived drops with no damage and no breaches.



Family of Purillex PFA Bottles

Savillex Technical Note

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Table 1: Drop Test Results

Bottle	Material	Results	Notes
1	PFA	No leaking; no paneling after thaw	
2	PFA	No leaking; no paneling after thaw	
3	PFA	No leaking; no paneling after thaw	
4	PFA	No leaking; no paneling after thaw	
5	PFA	No leaking; no paneling after thaw	
6	PFA	No leaking; no paneling after thaw	
7	PFA	No leaking; no paneling after thaw	
1	ETFE	No leaking; no paneling after thaw	
2	ETFE	No leaking; no paneling after thaw	
3	ETFE	No leaking; no paneling after thaw	
4	ETFE	No leaking; no paneling after thaw	
5	ETFE	No leaking; no paneling after thaw	
6	ETFE	No leaking; no paneling after thaw	
7	ETFE	No leaking; no paneling after thaw	

Conclusions

Evidence from this test protocol indicates that the Savillex 1 L PFA and ETFE bottles are suitable for freezing to -85°C and can withstand a drop from 36" onto concrete with no bottle damage and no loss of bottle integrity. This is a testament to the structural durability of fluoropolymer materials when exposed to cryogenic temperatures. It is also illustrative of the strength, reliability and seal integrity of the Purillex Bottle.

[Click here](#) to learn more about Purillex Bottles and shop online.

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