Savillex
Your Fluoropolymer Solutions Partner

Savillex Technical Note

Purillex® PFA & FEP Bottles - Designed for Biopharma Use

Summary

The adoption of disposable, or single-use technology (SUT), in biopharmaceutical manufacturing is growing rapidly[1]. SUT offers improved flexibility, reduced risk of contamination and lower costs. Bags made from laminated polymers are widely used as disposable containers for the freezing and storage of bulk drug substance (BDS), but where the properties of the BDS require it to be stored at -70°C, fluoropolymer (PFA or FEP) bottles are the only choice due to their very wide working temperature range. Since the bottle is in direct contact with the BDS for extended periods of time, and because of the high value of the BDS at point of use (just prior to final fill and finish), the bottle must be selected and validated with great care. While single-use bags have been purposely designed for biopharma manufacturing, the only available fluoropolymer bottles were designed originally for use in the chemical industry.

Purillex® Bottle Range

Savillex Purillex® PFA and FEP bottles are the first fluoropolymer bottles designed specifically for bioprocessing use. Manufactured in an ISO Class 7 cleanroom using unique stretch blow molding technology, they feature a biopharma industry standard GL45 closure and superior sealing performance. Purillex bottles also feature a consistent wall thickness to support gas transmission stability studies and come with regulatory and manufacturing lot certification. Savillex also produces small PFA vials for stability testing, reducing the amount of BDS required for validation. Savillex supports initiatives to safeguard the biopharma manufacturer's supply chain through audit visits, change notification and by working closely with its raw material suppliers.

Closure Design and Seal Quality

The GL45 closure, which is standard on all Purillex bottles from 100 mL to 2 L (33 mm closure on the 50 mL bottle), is a biopharma industry standard and can be modified to accept inserts for aseptic filling. The use of stretch blow molding enables more accurate and precise molding of the bottle neck and threads for a more secure, leak-free seal. A full 3.5 turns of thread engagement gives Purillex bottles greater thread engagement than any other fluoropolymer bottle and allows the large GL45 closure to be tightened more securely, which eliminates the need for a cap liner or a sealing insert and ensures long term seal integrity. The threads, neck and lip are injection molded at the preform stage, which eliminates the need for secondary machining of the lip. This results in an excellent seal and also eliminates the risk of burrs and flash on the lip that can generate particles.

Single Resin Grade

Due to the stretch blow molding process used, Purillex bottles are uniquely manufactured from a single grade of PFA (or FEP) resin. In stretch blow molding, the bottle is manufactured using a two step process: first, a "preform" is injection molded, which is then blown into the final bottle by a blow molding step. Because the bottle preform and closure are both injection molded, the same injection molding grade resin can be used for both components. This greatly simplifies testing and qualification. Conventional fluoropolymer bottles are extrusion blow molded, while the closure is injection molded. With this, two different grades of resin must be used for bottle and closure. In addition, only high purity grade, virgin resin is used for Purillex bottles: no reground, recycled waste polymer is ever added.

Particulates and Inclusions

The presence of particulates in SUT containers is a critical issue since most drugs stored in SUT containers are injectables and also subsequent filtration or processing to remove particulate contamination may not be feasible. When evaluating fluoropolymer bottles for SUT use, the BPSA White Paper, "Recommendations for Testing, Evaluation, and Control of Particulates from Single-Use Process equipment" is an excellent guide[2].

USP <788>, Particulate Matter in Injections, deals with the presence of extraneous, mobile or undissolved particles in the container (for example, loose atmospheric dust particles that have fallen into the container). While the prevention of particulate contamination is important, particularly for viable contaminants, fluoropolymer bottles for SUT use are typically inspected by the end-user prior to sterilization by autoclave (irradiation cannot be used to sterilize fluoropolymers since it breaks down the fluoropolymer). Of greater concern is what BPSA terms "embedded particulates" (inclusions). Embedded particulates are solid particulate contaminants embedded into the walls of the bottle during the molding step. This occurs with traditional extrusion blow molded fluoropolymer bottles due to the formation of carbon on the extrusion die, which can detach and become embedded in the bottle wall during molding. The stretch blow molding process used to manufacture Purillex bottles greatly reduces the formation of carbon particulates since the bottle preforms are injection molded prior to the blow molding step – no extrusion process is used.

Another potential source of embedded particulates is the trapping of airborne contamination, including viable contaminants, such as hairs, at the blow molding step. Purillex bottles are blow molded in an Class 10,000 ISO 7 cleanroom, and operators wear cleanroom coats, hair nets and overshoes, so the risk of airborne contamination during the blow molding step is significantly reduced. Because Purillex bottles are manufactured using stretch blow molding, the neck and lip are injection molded and require no secondary machining to produce a good seal. With traditional injection molding, the bottle lip must be machined to remove flash which is a source of intrinsic (or native) particulates. Finally, every Purillex bottle undergoes a visual inspection for embedded particulates and flaws prior to release. Bottles are also checked periodically during the production run to confirm wall thickness is in specification. Purillex bottles are sealed in LDPE bags inside the cleanroom immediately following inspection.

Wall Thickness

During end use validation of SUT containers, extensive stability testing must be performed to demonstrate that BDS quality and recovery is not impacted by the freeze/thaw cycles it undergoes during storage, transportation and use. Using the final 1 L or 2 L container for stability testing would be prohibitively expensive due to the large amount of BDS required, which may have a value of $100/mL or more at this stage of the manufacturing process. Small-scale containers are used, replicating as closely as possible the final container shape (or volume to surface contact area ratio), closure, material and headspace. Savillex produces a wide range of vials in PFA, and the 3 mL screw top PFA vial is typically used for stability studies. The 3 mL vial is available in the same PFA resin grade as Purillex bottles and available with manufacturing lot certification.

Purillex 1 L Bottle

Also of importance is the container wall thickness, since this impacts gas transmission rate. When shipped on dry ice, permeation of CO_2 through the bottle side wall may cause a pH shift in the BDS[3]. The 50 mL Purillex bottle was designed with the same nominal side wall thickness (0.050 in or 1.27 mm) as the 1 L and 2 L Purillex bottle sizes to facilitate stability studies on BDS pH change due to CO_2 permeation. By eliminating variability due to different side wall thickness, the quality of the stability testing is improved.

Physical Testing

Purillex bottles have undergone a range of physical testing to determine seal integrity and side wall strength under extreme conditions. Testing is comprised of drop tests from 4 ft, leak test at 1 bar internal pressure, vacuum resistance test and a pressure burst test. In comparison testing, Purillex bottles have been found to retain seal integrity at higher internal pressures than all other competitive bottles tested. This is due to the greater thread engagement and improved thread molding and lip surface quality through the stretch blow molding process. The practical benefit for biopharma use is greater protection of bottle contents over longer periods, under changing conditions and during transportation.

Certification and Validation Support

Purillex bottles have been certified by third party labs to meet and exceed the requirements of the following USP tests: USP <87>, <88>, <661> and <788>. Each lot is shipped with a certificate of conformance and is also tested externally using DSC to verify the fluoropolymer used. Bottles are shipped bagged and can also be provided sterilized and ready to use (RTU). Contact Savillex for more information on RTU bottle supply. Savillex has compiled extensive validation binders for both PFA and FEP bottles to assist in qualification: these are available under company non-disclosure agreement. In addition, Savillex partners with biopharma companies to provide full support of end user validation of Purillex bottles.

Quality, Supply Chain Assurance and Change Notification

Savillex has an established, documented quality system. The system is maintained as a means to ensure products produced by Savillex conform to internal or customer specified requirements. The Savillex quality manual defines a quality policy, general company structure and processes for maintaining the quality management system and is available on request. Savillex recognizes that the selection and validation of SUT represents a huge investment for its customers and partners with biopharma companies and strives to provide the highest level of supply chain assurance. Site audit visits to Savillex are welcomed. Savillex strictly implements change notification procedures for all its customers operating in GMP environments. Savillex also works closely with its suppliers and has supply contracts with both of the world's leading suppliers of fluoropolymer resins.

References

1. A journey from current stainless steel to future disposable freeze systems in clinical and large scale manufacturing. Goldstein et al, American Pharmaceutical Review, Dec 2012.
2. Recommendations for Testing, Evaluation, and Control of Particulates from Single-Use Process equipment, BPSA White Paper, 2014, www.bpsaalliance.org
3. Quality by design for freeze-thaw of biologics: concepts and application to bottles of drug substance. Kantor et al, American Pharmaceutical Review, May 2011.

Savillex
Your Fluoropolymer Solutions Partner
Savillex
10321 West 70th St. | Eden Prairie, MN 55344-3446 USA | Phone: 952.935.4100
Email: info@savillex.com | www.savillex.com