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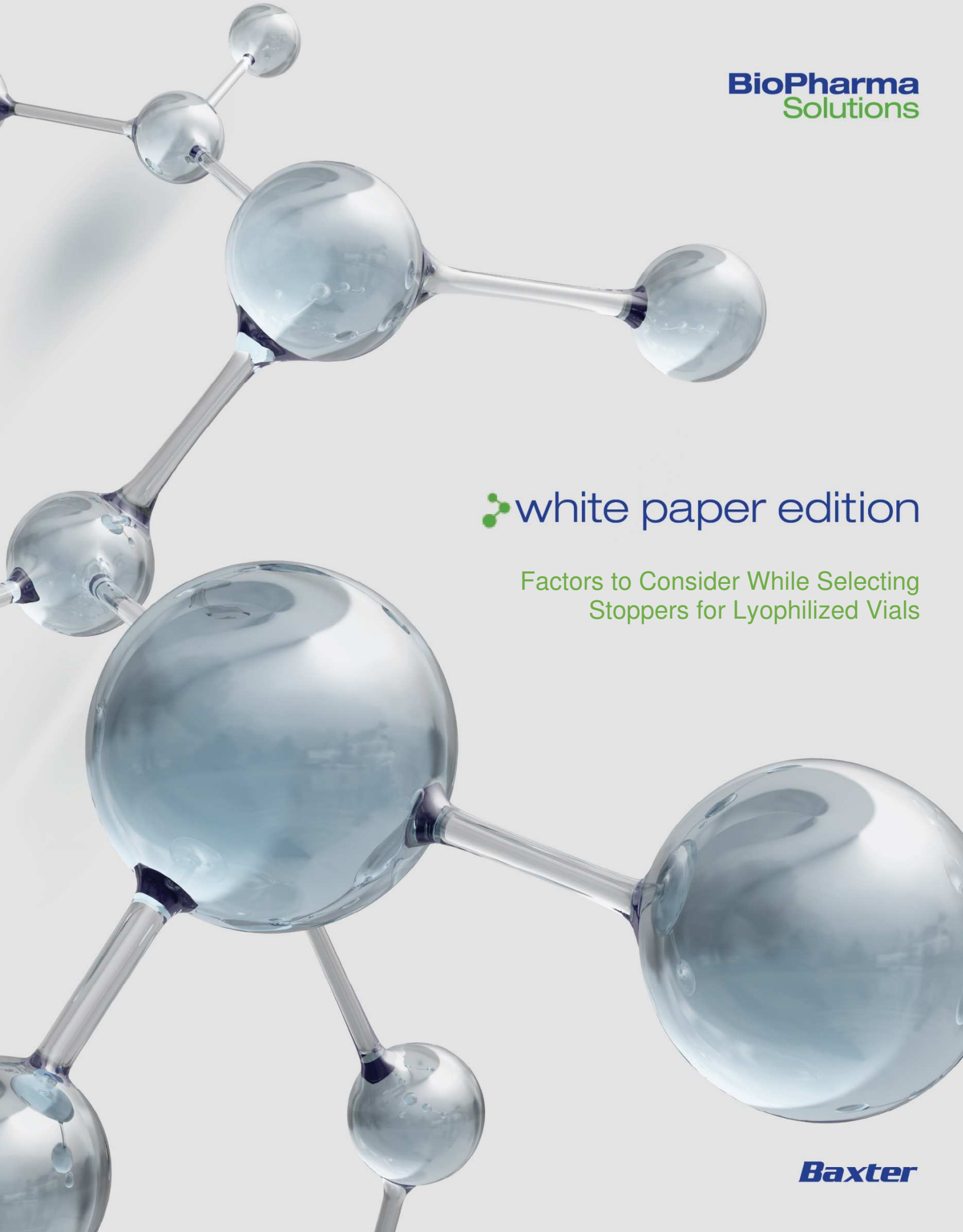
white paper edition

Factors to Consider While Selecting Stoppers for Lyophilized Vials



Baxter

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Introduction

Lyophilization is commonly employed for parenteral drugs that have poor stability in solution. In addition to formulation and process development, a robust container - closure (c/c) system is crucial for a successful lyophilized product.

Pharmaceutical rubber closures are an important component to maintain the integrity of the drug product. They act as a barrier against moisture, air, oxygen etc. Stoppers are partially placed on vials prior to transferring to the lyophilizer and the vials are completely stoppered at the end of the cycle at a pre-determined vacuum level. The vials are removed from the lyophilizer, capped, and sealed to ensure sterility.

Stoppers are vented and fall into 3 categories: single vented (igloo), dual vented, or 3-legged configurations (Figure 1).

Figure 1. IGLOO, 2-legged, and 3-legged Stoppers (20 mm)

The stopper design has no impact on the resistance of flow of water vapor during primary drying, but the IGLOO stoppers are preferred due to their ease of handling and good machinability since they tend to interlock less.

Parenteral stoppers are made of either natural or synthetic rubber. Natural rubber has good physical strength and withstands multiple stresses, but they are implicated in latex sensitivity. Butyl rubbers, made of copolymers of isobutylene with isoprene or butadiene, are the most commonly used elastomer due to their resistance to chemical attacks and aging. They have low permeability to air and moisture. Nitrile rubbers are oil and heat resistant but leaching of components of the formulation is significant. Chloroprene rubbers are similar in properties to butyl rubber but are more expensive. Silicone rubber is heat resistant up to 2500 °C but the process of siliconization comes with the risk of extractables and leachables contaminating the drug product. Siliconized stoppers also tend to stick to the freeze dryer shelf (Figure 2). The degree of stoppers sticking to the shelf is dependent on the compression force of the stoppering ram and the duration of compression.

Figure 2. Sticking of Stoppers to Dryer Shelves

Several ingredients are added to the rubber formulation during the manufacturing of stoppers. In addition to the elastomers described above, a curing agent is typically used that gives rubber its shape, elasticity, and resiliency. An antioxidant, such as phenol, is used to resist aging. Filler, pigments, accelerators, and plasticizers are also added. Once manufactured, the closures are rinsed with Water for Injection and depyrogenated.

Container closures are sterilized either by steam sterilization in an autoclave or by gamma irradiation using cobalt 60. The former method is more commonly used in the industry because it is less harsh. Stoppers are washed, rinsed, and heated to 121 °C in an autoclave for a maximum of 60 min followed by drying at 105 °C for up to 8 hours.

If siliconization is required for lubrication, it is performed after the washing process and prior to sterilization. A predetermined amount of silicone is added to the stopper washer during the wash cycle (Reference 1). Caution must be taken so that the right amount of silicone oil is applied. Over siliconization may result in adverse reaction with the product producing a hazy appearance. Under siliconization may result in stoppers clumping together (Figure 3).

Figure 3. Interlocking of Stoppers

To eliminate the need for siliconization, stoppers are coated with a film of tetrafluorethylene and ethylene (called FLUOROTEC) or polyethylene and tetrafluroethylene (called OMNIFLEX) (Reference 1). Several rubber formulations commonly used and currently available are summarized in (Table I).

Stoppers may be purchased directly from the manufacturer ready to use. These stoppers are already washed, siliconized, depyrogenated, and sterilized. Stoppers can also be purchased ready to sterilize that will require sterilization at the manufacturing facility.

One of the drawbacks of the stopper sterilization procedure is that the residual

moisture contents of stoppers increase during autoclaving and decrease during drying. The actual amount of water that a stopper retains, after sterilization, depends on the elastomer formulation and the drying time. During storage, this residual moisture can transfer from the stopper to the lyophilized cake. In some cases, storage humidity can permeate through stoppers into the freeze-dried solids. Consequently, it is important to follow appropriate sterilization protocol for stoppers so that moisture transmission is minimized.

The chemical composition of rubber closure formulations can play a role in determining the water retention capacity and the permeating ability. Vromans and Laarhoven evaluated the water absorption capacity of rubber closures and determined that rubbers with a low permeability took up significant amounts of water during sterilization (Reference 2).

Donovan *et. al.* investigated the effect of processing during sterilization on the moisture content of two commercially available 13-mm lyophilization stoppers (Reference 3). They concluded that the high moisture stoppers (HM, WEST 1816 V-36, bromobutyl) absorbed more water than the low moisture stoppers (LM, DAIKYO D777-1 V2-F195W butyl), hence the former required more drying time to achieve the same level of residual moisture content as that of the LM stoppers.

A more exhaustive evaluation of the effect of drying and moisture permeability on the increase in moisture content of lyophilized solids was conducted by Sasaki *et. al.* (Reference 4). They compared two different elastomeric stoppers (HM/D713 and LM/D777), using a formulation containing a protein drug and mannitol among other components. The formulation was lyophilized and placed on storage at 30 °C under varying humidity conditions: 0%, 65%, and 97%. The stoppers evaluated for the study were autoclaved at 121 °C for 20 minutes and dried at 80 °C for 2 or 24 hours.

They observed that the increase in the residual moisture content during the early stage of storage (0 to 93 days) was higher for the HM stopper fitted vials than for the LM stopper fitted vials. They attributed this increase to transfer of moisture from the closure to the freeze-dried solid and it correlated directly with the moisture absorbing ability of the stopper formulation. The LM stoppers have less moisture absorbing ability than the HM stoppers. The authors were able to control the moisture uptake by adequate drying of the stoppers during sterilization.

However, the moisture uptake trend was reversed during the later stage of storage (93 to 364 days). This was caused by the permeation of external moisture into the

solids through the stopper. They found that the stopper drying time did not have an impact on the moisture increase in vials during the second stage, indicating that it was more due to the moisture permeating ability of the stoppers. The DAIKYO D777 stoppers permitted more moisture to penetrate than the bromobutyl stoppers.

The R&D group at Baxter BioPharma Solutions in Bloomington, IN conducted experiments to better understand the mechanism of residual moisture migration into lyophilized solids on storage. The authors investigated a formulation containing mannitol (8% w/v), trehalose (2% w/v), and sodium chloride (225 mM) filled into 6 mL SCHOTT vials using a fill volume of 2 mL. The formulation was freeze dried and the vials were stoppered using either WEST 4416/50 (high moisture) or DAIKYO D777 (low moisture) stoppers. The lyophilized solids were placed in desiccators that were controlled at three relative humidity (RH) levels at ambient temperature. The RH levels investigated were 11% (prepared using a saturated solution of lithium chloride), 43% (saturated potassium carbonate solution), and 73% (saturated sodium chloride solution). Samples were removed after 3, 6, and 12 months of storage. The residual moisture levels of samples were determined using two methods: (a) near IR spectroscopy, a non-destructive method and (b) Karl Fischer coulometric method using methanol extraction. The stability data are provided in (Table II).

The data indicates that freeze dried vials fitted with WEST stoppers contained more residual moisture than the ones fitted with DAIKYO D777 stoppers. The water content increased during storage and the increase was more pronounced in the first 3 months of storage (1.5 to 2-fold) than at later timepoints when the increase was more gradual. No dependence of moisture uptake on the storage humidity was observed in the first three months.

After twelve months of storage, the moisture uptake appeared to correlate with the storage humidity condition for the DAIKYO D777 stoppers, with solids stored at higher RH levels exhibiting greater moisture uptake. This result points to the higher permeability nature of the DAIKYO D777 elastomeric formulation.

In conclusion, one should evaluate the sensitivity of a drug product to residual moisture excursions, storage conditions and duration when selecting stoppers for parenteral vials. In general, high moisture stoppers such as the WEST 4416/50 are best suited for large molecules during long-term storage due to their low moisture permeation ability. Low moisture stoppers like DAIKYO D777 could be considered for small molecules

that have a tighter residual moisture specification .

References

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Table I. Pharmaceutical Rubber Formulations

Rubber formulation	Manufacturer	Coatings available	Comments
4432/50	West	B2, Teflon®, Flurotec®	Preferred in USA. Low levels of metal extractables
4023/50	West	B2, Teflon®, Flurotec®	Preferred in EU. Low levels of metal extractables
D777-1 lyo	Daikyo	B2, Flurotec®	Preferred for lyo and protein formulations, hydrophobic, very low moisture, extremely low organic and metal ion extractables
D21	Daikyo	B2, Flurotec®	Low metal ion extractables and virtually no free sulfur content. Low gas and moisture permeability
D713	Daikyo	B2, Flurotec®	Good for oil based and hygroscopic materials. Extremely low free sulfur content, organic and metal ion extractables.
6720	Stelmi	None	Low residual moisture content, good for lyo. Excellent functional properties (self-sealing and resistance to coring).
6950 or 6955	Stelmi	None	Chlorobutyl-based, zinc-free high purity formulation, extremely low extractables
FM257	Helvoet	OmniFlex®	Standard bromobutyl compound, latex free
FM460	Helvoet	OmniFlex®	Low moisture bromobutyl, low extractables
FM457	Helvoet	OmniFlex®	For syringes, ultra-low extractables bromobutyl stopper

Table reproduced from Reference 1

Table II. Residual Moisture Data Summary

Stopper	Storage RH	% RM by NIR				% RM by KF			
		T0	T3m	T6m	T12m	T0	T3m	T6m	T12m
WEST	11%	0.42	1.06	1.06	1.82	0.32	0.79	0.69	0.89
			1.22	1.60	1.81		0.84	0.80	0.96
	43%		1.30	1.87	1.69		0.77	0.91	0.98
			1.34	1.51	1.60		0.73	0.81	1.01
	73%		1.29	1.42	1.75		0.46	0.81	1.04
			0.90	1.42			0.67	0.80	
DAIKYO D777	11%	0.16	0.36	0.45	0.54	0.21	0.35	0.34	0.38
			0.43	0.69	0.54		0.34	0.33	0.40
	43%		0.37	0.57	0.98		0.39	0.38	0.46
			0.47	0.60	0.74		0.38	0.40	0.48
	73%		0.37	0.56	0.97		0.41	0.41	0.53
			0.53	0.56	1.07		0.35	0.40	0.58

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