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Vial Containment Systems Based on Elastomer 4031/45 Gray

Performance Independent of Stopper Configuration

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Executive Summary

This report discusses results of two, two-year studies that indicate, for a properly-assembled vial containment system, good container closure integrity performance can be achieved with stoppers of a given elastomer, independent of configuration.

Vial, stopper and seal components are assembled to make a containment system for drug product storage, and these components are offered in an array of options varying by:

- **Vial** – glass type, configuration, size
- **Stopper** – elastomer type, configuration, size, coating/laminate
- **Seal** – materials of construction, configuration, size

Selection of components is based on the ability of the chosen system to protect the drug product through its shelf life.

Not every combination of vial, stopper and seal can be evaluated before selection due to prohibitive time pressures on drug development. But drug developers can evaluate the performance of selected key combinations which can subsequently inform likely performance of component combinations. Such performance knowledge enables an informed judgement at the outset of component selection. Note that each drug developer must make their own final evaluation of suitability for the intended drug product.

To this end, West has completed two major studies – both conducted over two years. The first considers a matrix of two well-established elastomer formulations, including 4031/45 Gray, with two well-established serum stopper configurations.[1, 2] *It was demonstrated that changing configuration had no effect on performance*. The second considers a variety of well-established elastomer formulations, including 4031/45 Gray, serum/lyophilization stopper configurations, and vial designs.[3, 4] *It was demonstrated that for an elastomer formulation, variations among stopper and vial had no effect on performance*.

The inference drawn from these studies is that, for a properly assembled system, for elastomer formulation 4031/45 Gray, good performance can be achieved independently of the stopper configuration or vial design.

STUDY 1 | Variation of Elastomer, Stopper Size, and Configuration

A two-year container closure integrity (CCI) evaluation of the systems described in Tables 1 and 2 was performed.[1, 2] Three stopper compressions were evaluated; glass vials were ISO straight wall. Images of stoppers are given in Figure 1.

TABLE 1 20 mm Serum Stopper Elastomer and Configuration Matrix

Elastomer	Configuration	
	S10-F451	ART 1343
4023/50 Gray	•	•
4432/50 Gray	•	•

TABLE 2 13 mm Serum Stopper Elastomer and Configuration Matrix

Elastomer	Configuration	
	S2-F451	ART 1358
4023/50 Gray	•	•
4432/50 Gray	•	•

FIGURE 1 Stoppers for Study 1

S10-F451 ART 1343 S2-F451 ART 1358

See Figures 2 and 3 for 20 mm systems and Figures 4 and 5 for 13 mm systems. For a given elastomer, changing stopper or size had no effect. Over two years, no variation in CCI performance was observed – by either tracer gas leak detection with helium (He leak) or laser-based gas headspace analysis with oxygen (O_2 headspace). This suggests strongly that for a given elastomer, variation of stopper configuration or size has no influence on performance, with proper system assembly. Note that for O_2 headspace studies, some exchange of atmosphere occured – i.e., O_2 concentration decreases as O_2 moves through the stopper outward, and concomitantly N_2 moves through the stopper inward. This is always observed as all polymers are gas permeable.

FIGURE 2

CCI Performance – 20 mm Serum Systems – Tracer Gas Leak Detection with Helium.

Data are reported as: [-log (He leak rate), mbar-L/s] so higher values represent lower leak rates. Data for low, medium, and high compressions are shown. Second y-axis represents residual seal force immediately after assembly.[1] Dotted line is Kirsch limit – often regarded as criterion for acceptable He leak performance.[5]

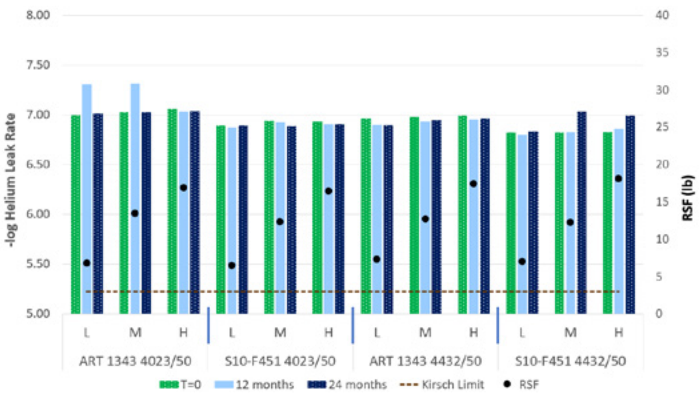


FIGURE 3

CCI Performance – 20 mm Serum Systems – Laser-Based Gas Headspace Analysis with Oxygen.

Systems were assembled in air and stored in a chamber filled with ca. 100% nitrogen. Data for low, medium, and high compressions are shown.[1]

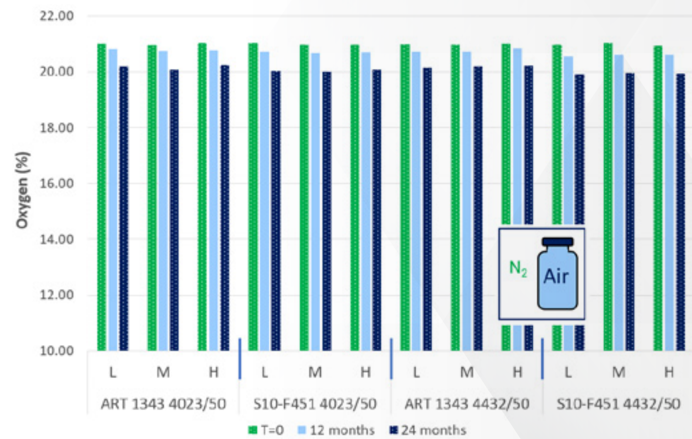


FIGURE 4

CCI Performance – 13 mm Serum Systems – Tracer Gas Leak Detection with Helium.

Data are reported as: [-log (He leak rate), cm3/s] so higher values represent lower leak rates. Data for low, medium, and high compressions are shown. Second y-axis represents residual seal force immediately after assembly.[2] Dotted line is Kirsch limit – often regarded as criterion for acceptable He leak performance.[5]

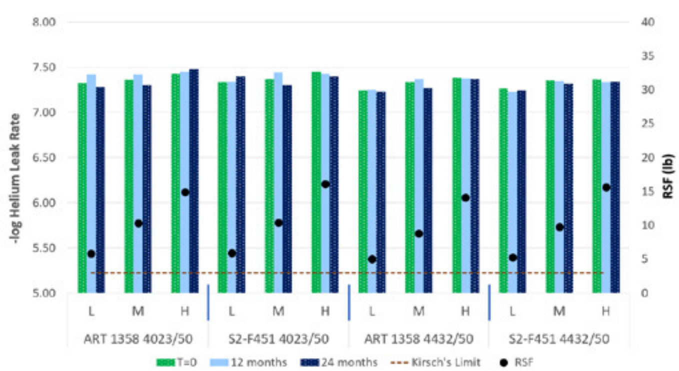
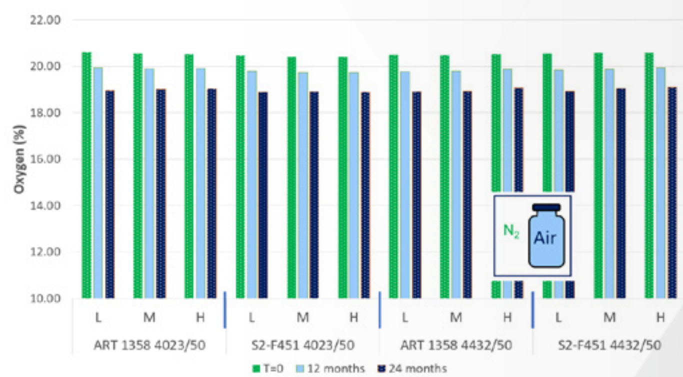


FIGURE 5

CCI Performance – 13 mm Serum Systems – Laser-Based Gas Headspace Analysis with Oxygen.

Systems were assembled in air and stored in a chamber filled with ca. 100% nitrogen. Data for low, medium, and high compressions are shown.[2]



STUDY 2 | Variation of Elastomer, Stopper Size and Configuration, and Vial Style

A two-year CCI evaluation of the systems described in Table 3 was performed.[3,4] Three stopper compressions were evaluated; glass vials were ISO standard. Images of stoppers are given in Figure 6.

TABLE 3 Stopper Configurations, Sizes and Vial Styles

Elastomer	Size (mm)	Type	Configuration	Vial Style	Vendor
4432/50 Gray	20	Serum	S-127	European	A
4023/50 Gray	20	Lyophilization	ART 1319	European	A
4031/45 Gray	20	Lyophilization	S-87-I	European	A
4023/50 Gray	20	Lyophilization	ART 1346	American	B
4023/50 Gray	13	Serum	ART 1358	Straightwall	A
4031/45 Gray	13	Serum	ART 1104	Straightwall	B
4031/45 Gray	13	Serum	V-35	American	B
4432/50 Gray	13	Lyophilization	V2-F451	Straightwall	B

FIGURE 6 Stoppers for Study 2

For a given elastomer, changing configuration or size, or vial style, had no effect on CCI. Over two years, no variation in CCI performance was observed – by either tracer gas leak detection with helium (He leak) or laser-based gas headspace analysis with oxygen (O_2 headspace). Similar to what was judged from **Study 1**, this strongly suggests that for a given elastomer, variation of stopper configuration/size or vial style has no influence on performance, with proper assembly.

Of particular focus were stoppers comprising 4031/45 Gray. See Figures 7 and 8. No variation in CCI performance was observed, in particular across three vial styles. Two points are noted: (a) for 20 mm system, He leak values are slightly lower – as observed always as there is greater surface area for He diffusion through the stopper as compared to 13 mm systems, and (b) as noted for Study 1, O_2 headspace study showed some exchange of atmosphere – i.e., O_2 concentration decreases as O_2 moves through the stopper outward, and concomitantly N_2 moves through the stopper inward. This is always observed as all polymers are gas permeable.

FIGURE 7 **CCCI Performance – Systems Comprising Elastomer 4031/45 Gray – Tracer Gas Leak Detection with Helium.** Data are reported as: [-log (He leak rate), mbar-L/s] so higher values represent lower leak rates. Data for low, medium, and high compressions are shown. Residual seal force was measured immediately after assembly.[3, 4]. Dotted line is Kirsch limit – often regarded as criterion for acceptable He leak performance.[5]

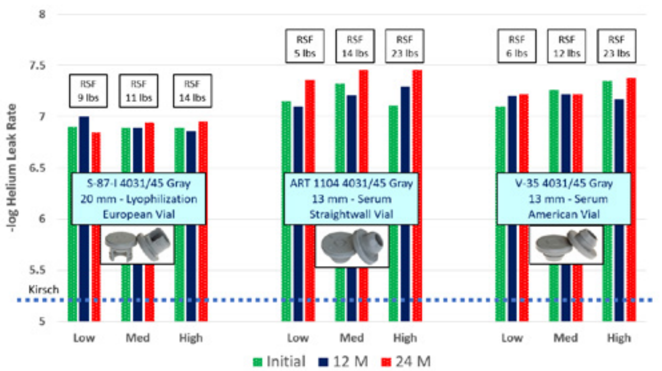
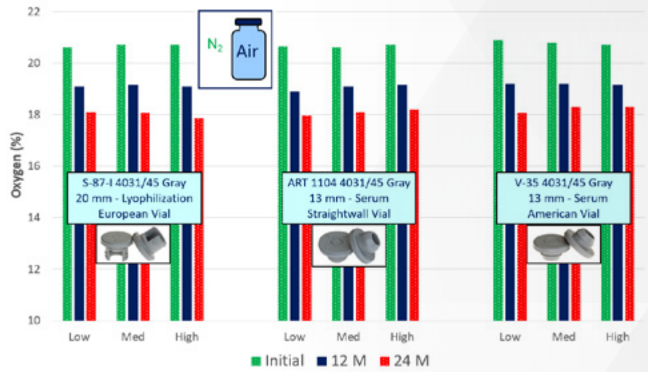


FIGURE 8 **CCI Performance – Systems Comprising Elastomer 4031/45 Gray – Laser-Based Gas Headspace Analysis with Oxygen.** Systems were assembled in air and stored in a chamber filled with ca. 100% nitrogen. Data for low, medium, and high compressions are shown.[3, 4]



Summary

For the two, two-year studies presented, for a given elastomer, in particular 4031/45 Gray, across stopper size, configuration and vial style, no performance variation was observed. This suggests strongly that the following 4031/45 Gray stoppers should perform well independent of vial style, with proper system assembly.

Configuration	Type	Size
V-35	Serum	13 mm
S-127	Serum	20 mm
ART 1071	Serum	20 mm
S-87-I	Lyophilization	20 mm
ART 1319	Lyophilization	20 mm

References

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