MITSUBISHI GAS CHEMICAL

OXYCAPT VIAL'S CONTAINER CLOSURE INTEGRITY AT -80°C WITH DRY ICE AND CO_2 BARRIER

In this article, Masashi Miura, Researcher, and Tomohiro Suzuki, Associate General Manager, both at Mitsubishi Gas Chemical, discuss the beneficial features of the OXYCAPT™ multilayer vial for biologics and gene and cell therapies, sharing recent study results highlighting OXYCAPT's performance at -80°C under dry ice conditions and its high carbon dioxide barrier compared with standard cyclo-olefin polymer.

OXYCAPT OVERVIEW

OXYCAPT™ is a multilayer plastic vial and syringe developed by Mitsubishi Gas Chemical (MGC), offering a number of advantageous qualities as a primary drug container, including:

- Excellent oxygen and ultraviolet (UV) light barrier
- Strong water vapour barrier
- Very low extractables
- High pH stability
- Low protein adsorption and aggregation
- High transparency
- High break resistance
- Easy disposability
- Lightweight material.

MGC continuously conducts studies to confirm these properties. The latest results of these will be shared in the later part of the article. Before that, the first half of this article will provide an overview of the OXYCAPT multilayer plastic vial (Figure 1). The material consists of three layers – the drug contact layer and the outer layer are made of cyclo-olefin polymer (COP) and the oxygen barrier layer is made of MGC's novel polyester (Figure 2).

MGC recently obtained a report on the environmental impact of glass and plastic containers for medical use from a Japanese research company. The report shows that plastic containers for medical use are much more environmentally friendly compared with glass containers.

Figure 1: OXYCAPT multilayer plastic vial.

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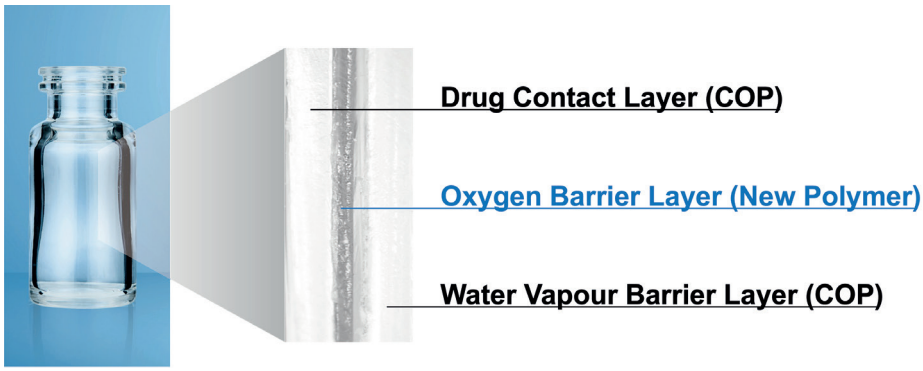

Figure 2: Multilayer structure of OXYCAPT.

"The oxygen barrier of an OXYCAPT vial is about 20 times better than that of a COP monolayer vial."

For example, the carbon footprint, nitrogen oxides emissions, sulfur oxides emissions and water consumption associated with plastic containers for medical use are several times smaller than those of their glass equivalents.

OXYCAPT provides an excellent oxygen barrier. For example, the oxygen barrier of an OXYCAPT vial is about 20 times better than that of a COP monolayer vial. Furthermore, OXYCAPT provides an excellent UV barrier. While about 70% of 300 nm UV light transmits through glass and COP, only 1.7% transmits through OXYCAPT. MGC has confirmed that this feature contributes to the stability of biologics.

While OXYCAPT cannot reach the performance of glass with respect to acting as a water vapour barrier, its properties are similar to those of COP, which has been used for injectable drugs for a long time. This means that OXYCAPT easily meets the requirements of a water vapour barrier set out by the ICH guidelines.

Studies have shown an extremely low level of extractables from OXYCAPT. One study was conducted to confirm the levels of volatile, semi-volatile and non-volatile impurities from OXYCAPT. Water and four solutions (50% ethanol, sodium chloride, sodium hydroxide and phosphoric acid) were selected, and impurities were measured by gas chromatography mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the control, impurities were not detected in the OXYCAPT containers. A second study confirmed that inorganic extractables levels from OXYCAPT were similar to those from COP, which is well known for being an extremely pure polymer with a better extractables profile than Type 1 glass. Lower levels of inorganic extractables are known to contribute to better pH stability in drug products.

The OXYCAPT vial is produced by co-injection blow-moulding technology. MGC has also developed inspection methods for testing the oxygen barrier layer. All the containers are fully inspected by state-of-the-art inspection machinery.

MGC can offer bulk vials and ready-to-use (RTU) vials, with its RTU products provided in standard nest and tub or tray formats. The nest and tub are mainly sterilised using gamma rays. There are 2, 6, 10 and 20 mL variants for vials. MGC is willing to provide samples for initial testing free of charge.

Each polymer meets the requirements of US Pharmacopeia (USP) regulations USP <661>, USP <87> and USP <88>, as well as those of the European Pharmacopoeia, and has been filed in the US FDA's drug master file (DMF). The vials are also compliant with each pharmacopoeia and have been filed in the DMF.

The primary target market for OXYCAPT is the therapeutic application of biologics. As mentioned in ICH Q5C (Stability of Biotechnological/Biological Products), oxidation is one of the causes of protein instability. As such, the oxygen and UV barrier properties of OXYCAPT will definitely contribute to the stability of biologics stored within. Furthermore, some drug developers have recently started evaluating the OXYCAPT vials for their gene and cell therapies; the RTU vial is sterilised by gamma radiation, making it ideal for protein-based drugs.

CONTAINER CLOSURE INTEGRITY AT -80°C

All pharmaceutical containers must maintain integrity against microbial contamination and have a gas barrier when a drug is sensitive to oxygen or carbon dioxide (CO_2). Figure 3 shows a typical scheme of storage and transportation for gene therapy. During storage and transportation, packages, including vials, are exposed to temperatures of around -80°C in a deep freezer or dry ice, which is a potential risk to container closure integrity (CCI) due to differences in the coefficient of thermal expansion (CTE) of the vial and rubber closure materials.

The CCI of Type I glass vials is particularly at risk from very low temperatures compared with plastic vials because the CTE of typical Type I glass is a factor of 10 smaller than that of rubber, including a halogenated butyl rubber. On the other hand, standard plastic vials have a potential risk of CO_2 transmission

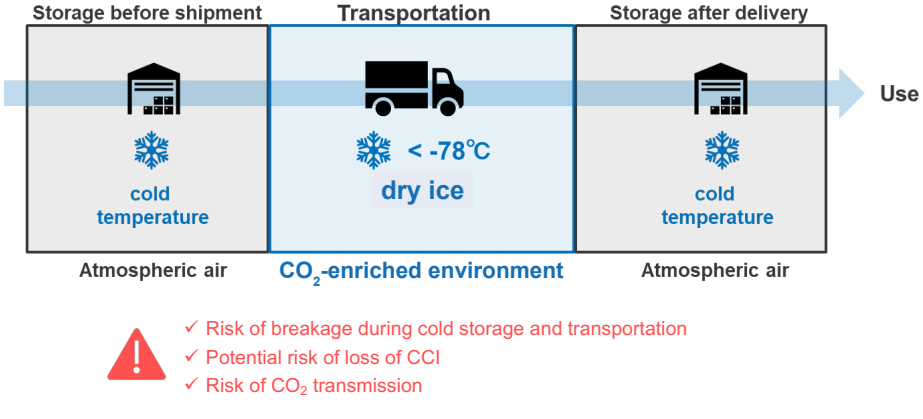

Figure 3: Typical scheme of storage and transportation for gene therapy.

Entry	Vial configuration	Vial	Rubber Closure	Aluminum seal cap
1	OXYCAPT/Rubber closure 1	OXYCAPT-P 10 mL vial	Bromo butyl rubber	Standard one with closure 1
2	OXYCAPT/Press-on-cap closure 2	OXYCAPT-P 10 mL vial	Press-on-cap closure	
3	OXYCAPT/Rubber closure 1/Positive control	OXYCAPT-P 10 mL vial	Bromo butyl rubber	Standard one with closure 1

Table 1: Test sample combinations of OXYCAPT vial and rubber closures.

when in storage with dry ice. Based on MGC's calculation by measurement of the transmission rate of CO_2 through a polymer film, OXYCAPT has a CO_2 barrier more than 20 times better than comparable COP monolayer vials. This means that the OXYCAPT vial has the potential to significantly contribute to protecting drugs, including biologics and gene and cell therapies, when they are in transport with dry ice.

To examine this potential benefit further, MGC performed a CCI test with dry ice. Table 1 shows the test sample combinations of OXYCAPT vial and rubber closures. Rubber closure 1 is a typical closure made of bromo butyl rubber with a glass transition temperature of -65°C. MGC also prepared press-on-cap closures and OXYCAPT's positive control with a fine hole of a 5 µm nominal diameter.

Figure 4 shows the test procedure, which includes storage in a deep freezer and an insulation box with dry ice. First, all the vials, closures and aluminium seals were inserted into a chamber where the air was replaced with nitrogen, then they were assembled by hand in the chamber. After preparing the samples, MGC measured the partial pressure of CO_2 in the vials' headspace for all the samples (T_0). The samples were then stored in a deep freezer at -80°C for seven days. After storage in the freezer, the CO_2 pressure of the headspace was measured (T_1). Next, the remaining samples were immediately inserted into an insulation box that was filled with 30 kg of dry ice, as shown in Figure 5. After storage in the CO_2-enriched environment, CO_2 pressure in the headspace was measured (T_2).

Headspace pressure of CO_2 was measured with an FMS-Carbon Dioxide, manufactured by LIGHTHOUSE Instruments (VA, US). The instrument is based on frequency modulation spectroscopy (FMS), which is a non-destructive method. Table 2 shows the sample number for each measurement time

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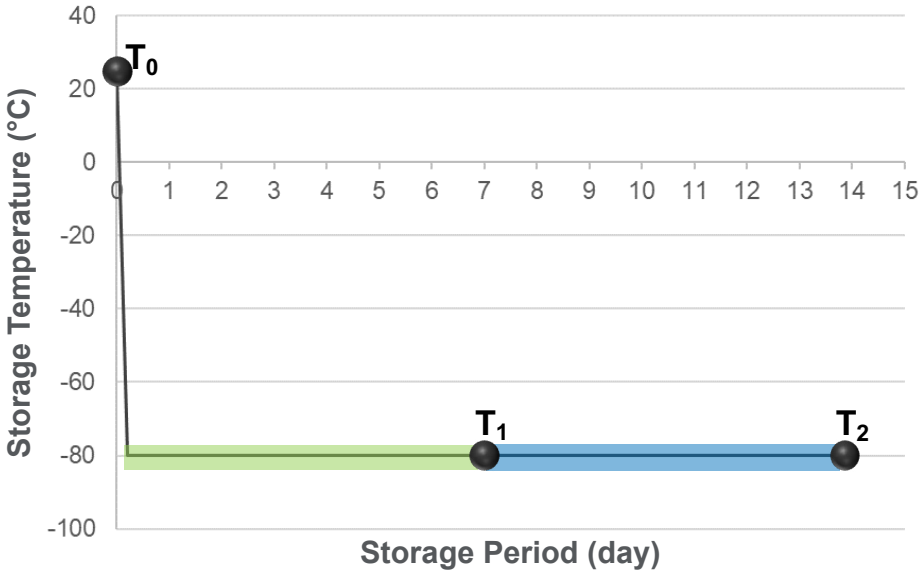


Figure 4: Test procedure of storage in deep freezer and insulation box with dry ice.

Figure 5: Dry-ice blocks in insulation box.

Entry	Vial	Stopper	T_0 The number of all samples	T_1 (7 days)	T_2 (7 + 7 days)
1	OXYCAPT	Rubber closure 1	40	20	20
2	OXYCAPT	Press-on-cap closure 2	40	20	20
1'	OXYCAPT, Postive control	Rubber closure 1	10	5	5

Table 2: Sample number for each measurement time point.

point. The measured vials were disposed of after the measurements at T_1 and the remaining ones were measured at T_2.

At temperatures lower than -65°C, bromo butyl rubber loses its elastic properties, which may lead to loss of airtightness at the interface between vial and rubber closure. Therefore, maintaining a temperature inside the insulation box of under -65°C is crucial for measuring the leakage precisely in this test. Figure 6 shows a temperature log inside the insulation box during the test, which was kept below -70°C for seven days.

Figure 7 shows the results of headspace CO_2 pressure for Entries 1, 2 and 1'. Regarding OXYCAPT positive control of Entry 1', the mean value of CO_2 pressure was 183 Torr at T_2 under a CO_2-enriched environment. However, there was no CO_2 ingress at T_1, as the initial seven-day storage was conducted under atmospheric conditions without dry ice. On the other hand, CO_2 ingress was not observed in either combination of OXYCAPT and the two types of closure (Entry 1 and Entry 2), even at T_2. This study demonstrated that OXYCAPT has an excellent CCI under a CO_2-enriched environment for seven days.

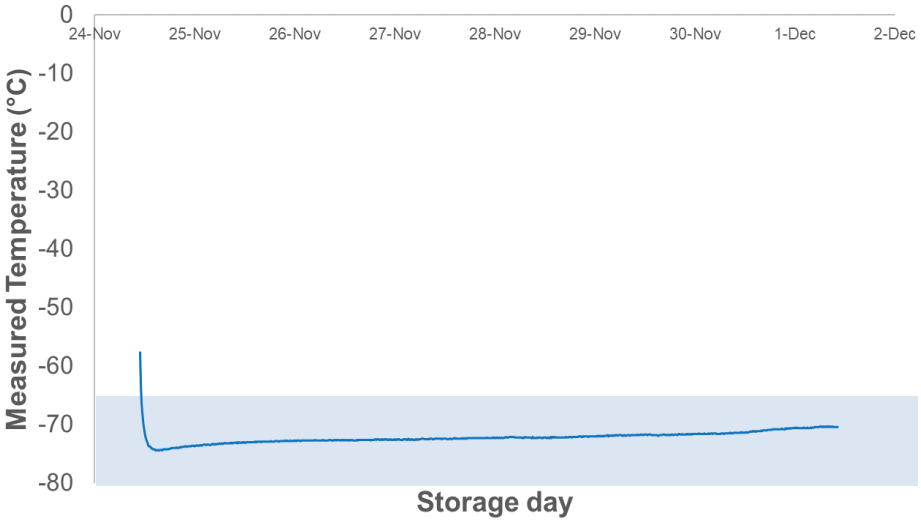


Figure 6: Logging temperature data in the insulation box.

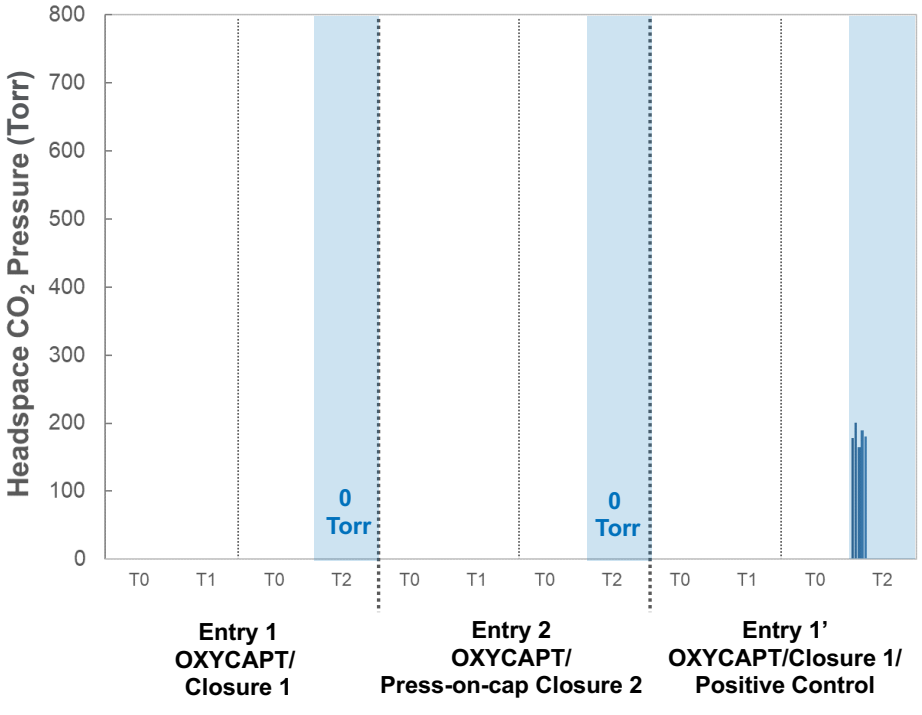


Figure 7: Headspace CO_2-enriched pressure for Entry 1, 2 and 1'.

There are several factors that can affect CCI for a combination of vials and closures, including capping force and type of closure, among others. In addition, CO_2 transmission is potentially observed in long-term storage with dry ice and an increase in temperature during storage. MGC intends to devise and perform additional CCI tests to clarify the efficiency of OXYCAPT vials compared with other plastic and glass vials. Furthermore, MGC is also planning to conduct similar studies at -180°C to confirm the effectiveness for gene and cell therapies.

CO_2 BARRIER OF OXYCAPT

CO_2 molecules can permeate through polymers and get into a vial's headspace, affecting drug stability. As the rate of CO_2 transmission is different between polymer materials, MGC performed some related studies using OXYCAPT and COP vials. OXYCAPT and commercially available COP 10R vials were prepared with bromo butyl rubber (BBR) and aluminium seal closures. Firstly, all the vials and BBR and aluminium seals were placed in a nitrogen chamber for a couple of days. Secondly, the vials were sealed with the closures using

a hand-crimper in a nitrogen chamber. Thirdly, these vials, filled with nitrogen gas, were placed in a box filled with CO_2 and stored at 23°C.

Figure 8 shows the results of headspace CO_2 partial pressure of OXYCAPT and COP vials. Although the CO_2 partial pressure of COP vials immediately rose, reaching around 700 torr in 60 days, the OXYCAPT vials were able to keep CO_2 partial pressure to very low levels.

MGC also calculated the CO_2 transmission rate of OXYCAPT and COP vials by using the test results of CO_2 partial pressure. While only 0.018 cm^3 of carbon dioxide transmitted through OXYCAPT 10R vials per day at 23°C, 0.423 cm^3 transmitted through 10R COP vials (Figure 9). This result demonstrates that the CO_2 barrier of OXYCAPT is more than 20 times better than that of standard COP.

CONCLUSION

These latest results have contributed to the ongoing studies verifying OXYCAPT's superior properties for biologics and gene and cell therapies. In addition to the advantages of COP, such as a strong water vapour barrier, high break resistance, very low extractables and low protein adsorption, OXYCAPT also provides strong oxygen and UV light barriers. In particular, the excellent CO_2 barrier of OXYCAPT is very useful for the stability of gene and cell therapies stored with dry ice. MGC believes that OXYCAPT offers a multitude of benefits to the rapidly growing field of biologics and gene and cell therapies.

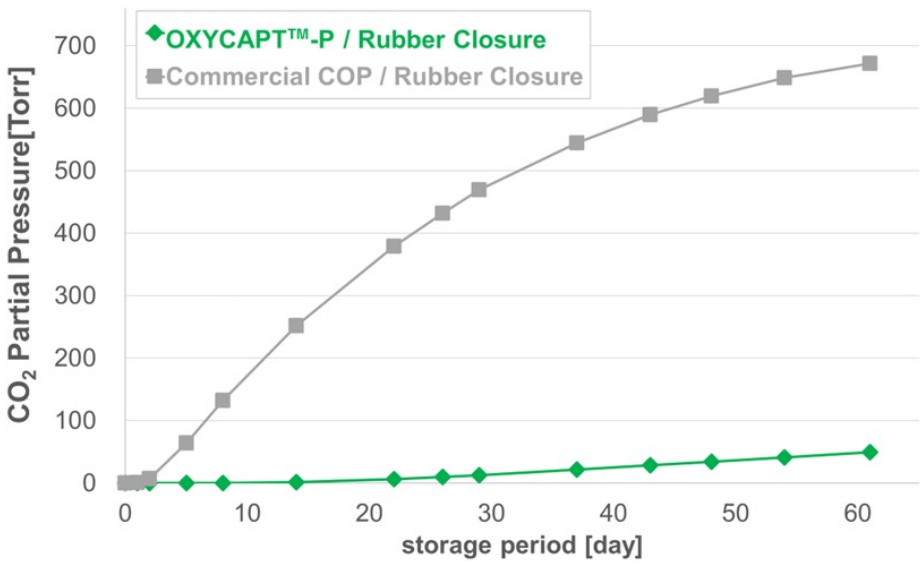


Figure 8: Headspace CO_2 partial pressure of OXYCAPT and COP vials.

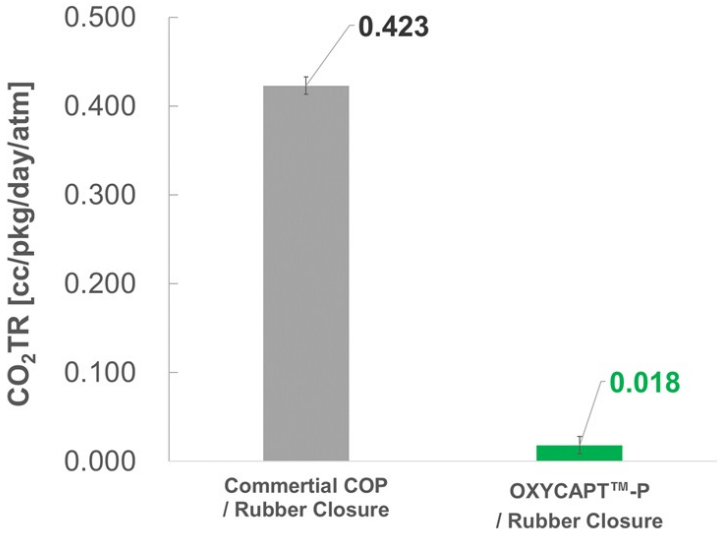


Figure 9: CO_2 transmission rate of OXYCAPT and COP vials.

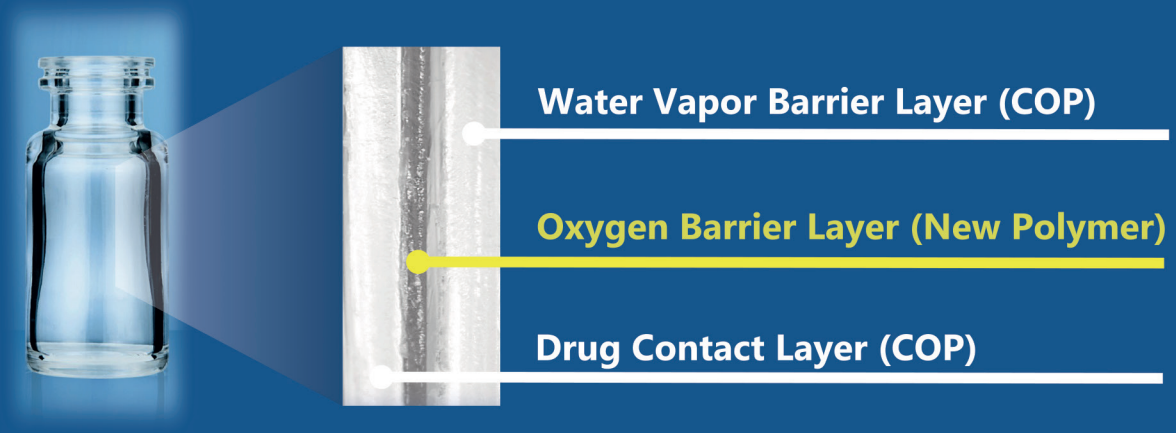
ABOUT THE AUTHORS

Masashi Miura is a Researcher at Mitsubishi Gas Chemical's Hiratsuka Research Laboratory. He gained a diploma in Science in 2020 and a master's degree in 2022 from Osaka University (Japan). At university, he majored in Applied Chemistry and studied crystalline porous materials. He has worked for Mitsubishi Gas Chemical since April 2022, joining a development team for multilayer plastic vials and syringes for biologics in May 2022.

Tomohiro Suzuki graduated from Waseda University (Japan) in 1997 and joined MGC in 1998. He belonged to the Oxygen Absorbers Division until 2011, after which he was transferred to the Advanced Business Development Division in 2012 to be a member of the OXYCAPT development team. Since then, he has been in charge of marketing for the OXYCAPT vial and syringe. His current position is Associate General Manager.

OXYCAPT™ Multilayer Plastic Vial

Multilayer Structure



- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Low Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Gamma-sterilized Vial
- For Biologics & Regenerative Medicine
- Customizable

2, 6, 10, 20mL Vial

Nest & Tub for Vial

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