MITSUBISHI GAS CHEMICAL

UPDATE ON OXYCAPT™ MULTILAYER PLASTIC VIAL AND SYRINGE

In this article, Hiroki Hasegawa, Researcher, and Tomohiro Suzuki, Associate General Manager, both of Mitsubishi Gas Chemical, discuss the advantages of OXYCAPT™ multilayer plastic vial and syringe, which combine the benefits of cyclo-olefin polymer with excellent oxygen and UV barrier properties. In particular, the authors focus on recent studies that highlight OXYCAPT's very low levels of extractables.

Compared with five years ago, the use of plastic has become much more popular in the pharma industry. As a result, more and more customers have started considering plastic vials or syringes. Although glass used to be considered the best option to protect drugs from oxygen and other negative factors, some critical issues have been pointed out with it, such as delamination, pH shift and breakage. In particular, these problems are especially prevalent with protein-based drugs, such as biologics and gene and cell therapies, that are stored at low or ultra-low temperatures.

> "MGC has developed OXYCAPT™ multilayer plastic vial and syringe, which provides the myriad advantages of COP along with high oxygen and UV barrier properties."

To avoid these problems, cyclo-olefin polymer (COP) vials and syringes are sometimes used for such biologics. COP has some excellent features – including very low levels of extractables, low protein adsorption, high break resistance and excellent pH stability – but it is obvious that its oxygen and ultraviolet (UV) barrier properties are very poor. To overcome the situation, Mitsubishi Gas Chemical (MGC) has developed OXYCAPT™ multilayer plastic vial and syringe, which provides the myriad advantages of COP along with high oxygen and UV barrier properties (Figure 1).

Figure 1: The OXYCAPT™ multilayer plastic vial and syringe.

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OXYCAPT™ OVERVIEW

OXYCAPT™ consists of three layers – the inner layer in contact with the drug product and the outer layer are made of COP, while the middle oxygen barrier layer is made of MGC's novel polyester (Figure 2). Thanks to this multilayer structure, OXYCAPT™ is able to provide the following key benefits:

- Excellent oxygen barrier
- High water vapour barrier
- Excellent UV barrier
- Very low levels of extractables
- High pH stability
- Low protein adsorption and aggregation
- Silicone-oil free barrel
- High transparency
- High break resistance
- Easier disposability
- Light weight.

There are two variants of OXYCAPT™ available – OXYCAPT-A and OXYCAPT-P. OXYCAPT-A has achieved a glass-like oxygen barrier. According to some of MGC's internal studies, OXYCAPT-A can keep a lower oxygen concentration in its headspace than Type I glass, thanks to its oxygen absorbing function. While OXYCAPT-P lacks an oxygen absorbing function, it provides an excellent oxygen barrier; the oxygen barrier of OXYCAPT-P Vial is about 20 times better than that of a COP monolayer vial (Figure 3).

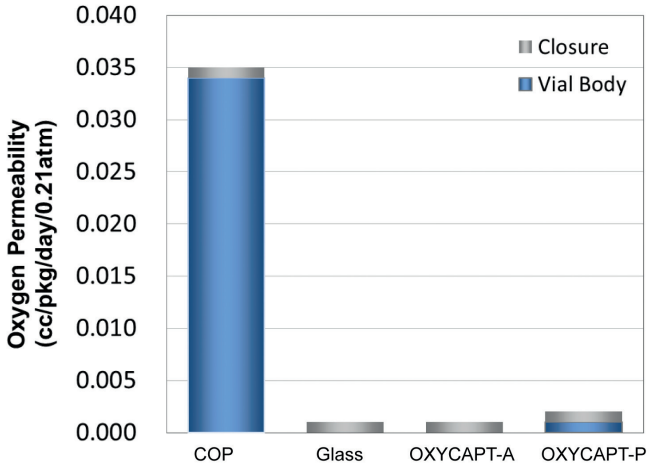


Figure 3: Comparison of the oxygen barrier properties of glass, COP, OXYCAPT-A and OXYCAPT-P.

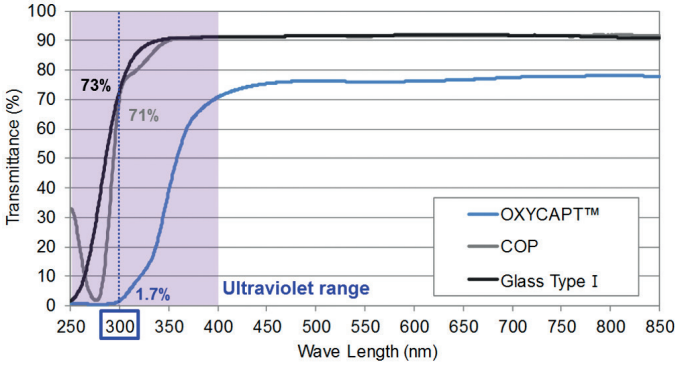


Figure 4: Comparison of the percentage of 300 nm UV light transmitted through Type I glass, COP and OXYCAPT™.

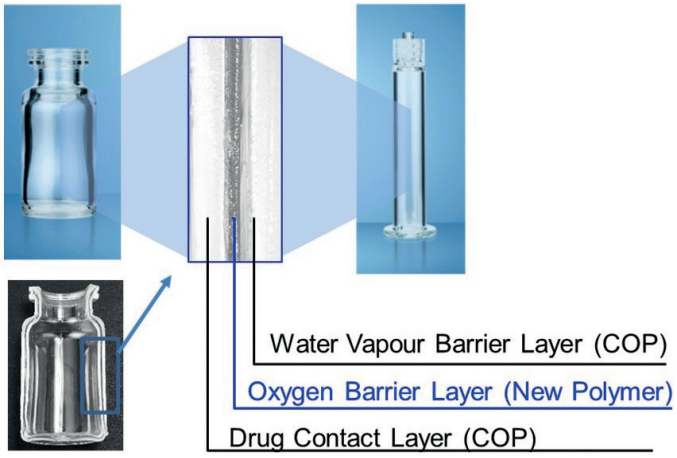


Figure 2: Multilayer structure of OXYCAPT™.

OXYCAPT™ also has excellent UV barrier properties. For example, although about 70% of 300 nm UV light transmits through glass and COP, only 1.7% of 300 nm UV light transmits through OXYCAPT™ (Figure 4). MGC has confirmed that this feature contributes to the stability of biologics.

However, when it comes to acting as a barrier to water vapour, OXYCAPT™ cannot reach the performance of glass. However, its properties in this regard are similar to those of COP, which has seen extensive use in primary containers for injectable drugs and easily meets the water vapour barrier requirements set out by ICH guidelines.

MGC conducted a pair of studies to demonstrate OXYCAPT's extremely low levels of extractables. The first study was conducted to confirm volatile, semi-volatile and non-volatile impurities from OXYCAPT™. Five solvents – distilled water, 50% ethanol, NaCl, NaOH and H3PO4 – 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, no impurities were detected in any of the OXYCAPT™ containers. The second study was conducted to confirm inorganic extractables from OXYCAPT™. The level of extractables demonstrated was similar to that typical of COP, which is well-known as an extremely pure polymer, and lower than that of Type I glass.

OXYCAPT™ vial and syringe are produced by co-injection moulding technology. Although this technology has been used in the production of beverage bottles for many years, MGC is the first company to succeed in applying it for the production of multilayer plastic syringes. MGC has also developed inspection methods for testing the oxygen barrier layer. All of the containers are 100% inspected by state-of-the-art inspection machinery.

> "The target therapeutic application of OXYCAPT™ is biologics. As ICH Q5C mentions, oxidation is one of the primary causes of protein instability. As such, the high oxygen and UV barrier properties of OXYCAPT™ contribute directly to the stability of biologics."

Type	Volume	ISO	Parts	Option
Vial	2 mL	ISO 8362-1	Vial	Bulk or RTU
	6 mL	ISO 8362-1	Vial	Bulk or RTU
	10 mL	ISO 8362-1	Vial	Bulk or RTU
	20 mL	ISO 8362-1	Vial	Bulk or RTU
Syringe	1 mL long	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU
	2.25 mL	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU

Table 1: MGC's OXYCAPT™ product portfolio.

CURRENT PRODUCT OFFERING

MGC can offer bulk vials, ready-to-use (RTU) vials and RTU syringes. Regarding the RTU products, vials and syringes are provided in ISO-standard nest and tub formats. The nest and tub are primarily sterilised using gamma radiation. There are 2, 6, 10 and 20 mL sizes for vials, and 1 mL long and 2.25 mL sizes for syringes (Table 1). MGC is happy to provide samples for initial testing free of charge.

Each polymer meets the requirements set out by United States Pharmacopeia (USP) <661>, USP <87>, USP <88> and all relevant European Pharmacopoeia (EP) regulations. Furthermore, each polymer has been filed in the US FDA's drug master file (DMF). The vials and syringes also comply with the USP and EP, and have FDA DMF numbers. Regarding the syringes, the products are produced and controlled in accordance with ISO 13485.

"The latest studies have shown an outstanding characteristic of OXYCAPT™ – extremely low levels of extractables."

The target therapeutic application of OXYCAPT™ is biologics. As ICH Q5C "Stability of Biotechnological/Biological Products" mentions, oxidation is one of the primary causes of protein instability. As such, the high oxygen and UV barrier properties of OXYCAPT™ contribute directly to the stability of biologics. Customers have also recently started evaluating OXYCAPT™ vials for their gene and cell therapies. MGC's RTU vials and syringes sterilised by gamma radiation are ideal for these protein-based drugs.

In addition, MGC believes that OXYCAPT™ is well suited to adrenaline, as it is well-known to be an oxygen-sensitive drug. Furthermore, as glass syringes suffer more from breakages than plastic ones, they are inherently less suitable for emergency drugs. As such, some suppliers are

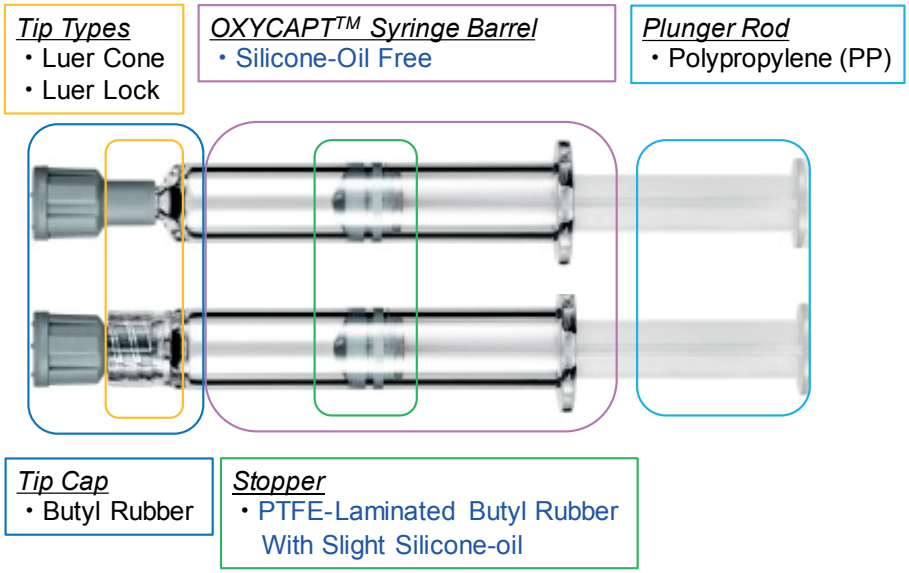


Figure 5: Components of an OXYCAPT™ syringe.

investigating plastic for the development of new pen injectors for emergency applications.

EXTRACTABLES STUDY FINDINGS

The latest studies have shown an outstanding characteristic of OXYCAPT™ – extremely low levels of extractables. An organic and elemental extractables study, which was performed in collaboration with an outsourcing pharmaceutical company, was conducted using MGC's container closure system (CCS) comprised of a 1 mL long OXYCAPT-P syringe, custom-ordered PTFE laminated butyl rubber stopper, and a normal butyl rubber tip cap (Figure 5).

Analytical method	Solution	AET (ppm)	Compounds found above AET
HS-GC-MS	0.1% PS-20	0.3	**No compound detected above AET**
	pH 3 buffer		
	pH 10 buffer		
GC-MS	0.1% PS-20	1.5	**No compound detected above AET**
	50% ethanol		
	pH 3 buffer		
	pH 10 buffer		
	50% ethanol by speed vac		
LC-UV-MS	0.1% PS-20	1.5	**No compound detected above AET**
	50% ethanol		
	pH 3 buffer		
	pH 10 buffer		
	50% ethanol by speed vac		

- AET was decided by calculation with reference of butylated hydroxytoluene (BHT) for GC-MS and LC-UV-MS or toluene for HS-GC-MS.
- As to 50% ethanol, the different sample work-up procedures were conducted to target different polarities.
- In case of '50% ethanol' in 'Solution', extraction was conducted in sample work-up to target non-polar and volatile compounds.
- In case of '50% ethanol by speed vac' in 'Solution', evaporation was conducted in sample work-up to target polar and less volatile compounds.

Table 2: Results of an organic extractables study using the OXYCAPT™ syringe CCS.

In order to detect and quantify organic analytes, volatile compounds were measured by headspace gas chromatography-mass spectrometry (HS-GC-MS). Moreover, non-polar, volatile and semi-volatile compounds were measured by GC-MS, whereas LC-UV-MS was used to detect compounds with varying polarity and volatility. Furthermore, with the OXYCAPT™ CCS, levels of the elemental impurities specified in ICH Q3D plus tungsten were detected and quantified by inductively coupled plasma mass spectrometry (ICP-MS).

These studies were conducted by a 48-hour incubation at 50°C of the OXYCAPT™ CCS with four different formulations:

- 0.1% aqueous polysorbate 20 (PS-20)
- 0.1 M phosphate buffer at pH 3
- 0.1 M phosphate buffer at pH 10
- 50% ethanol solution.

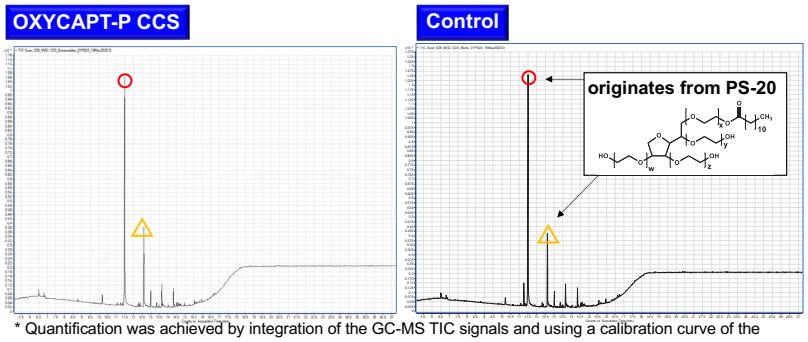
These extraction solutions cover those outlined in the latest draft of USP <665>. After incubation, a sample work-up for each solvent and analysis method was performed. Then it was confirmed whether there were any organic extractables that exceeded the analytical evaluation threshold (AET) using analytical devices. Each AET of HS-GC-MS, GC-MS and LC-UV-MS was determined by calculation with respect to the safety concern threshold (1.5 µg), filling volume of the syringe, maximum number of syringes administered per day and the concentration factor due to sample work-up. The results of analysis with HS-GC-MS, GC-MS and LC-UV-MS all showed no organic compound exceeded the AET with the OXYCAPT™ CCS (Table 2).

Figure 6 shows the GC-MS chromatogram with 0.1% aqueous PS-20. As shown in this graph, some peaks that originate from PS-20 used in the sample work-up exceeded the AET (1.5 ppm) in both the OXYCAPT™ CCS and control. However, there was no peak originating from OXYCAPT™ CCS above the AET. Furthermore, Figures 7 and 8 show the LC-UV and HS-GC-MS chromatograms for 0.1% aqueous PS-20, respectively. As is the case with GC-MS, there were no peaks originating from the OXYCAPT™ CCS detected in either analysis. Moreover, there were no peaks originating from OXYCAPT™ CCS detected with 0.1 M phosphate buffer pH 3, 0.1 M phosphate pH 10 or 50% ethanol either.

In the study with ICP-MS, no elemental impurities exceeded their permitted daily

No volatile and semi-volatile compound that originates from OXYCAPT™ CCS was detected above AET (1.5 ppm) in 0.1 % PS-20 solution.

- The chromatogram with OXCAPT™ CCS is almost same with the control.
- Signals exceeding above AET originate from PS-20 used in the sample work-up*.

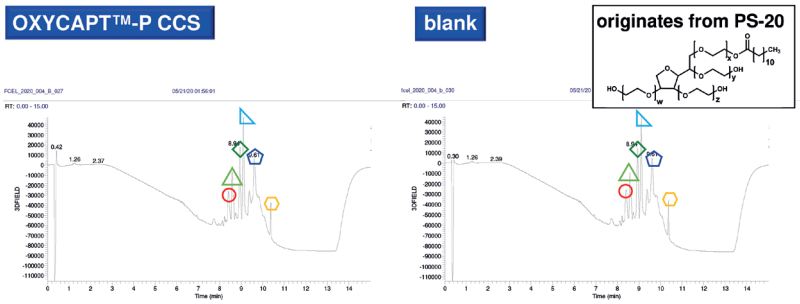


* Quantification was achieved by integration of the GC-MS TIC signals and using a calibration curve of the external reference BHT.

Figure 6: GC-MS chromatogram of OXYCAPT™ CCS and control with 0.1% aqueous PS-20 solution.

No compound with varying polarity and volatility that originates from OXYCAPT™ CCS was detected above AET (1.5 ppm) in 0.1 % aqueous PS-20.

- The chromatogram with OXCAPT™ CCS is almost same with the control.
- Signals exceeding above AET originate from PS-20 used in the sample work-up*.

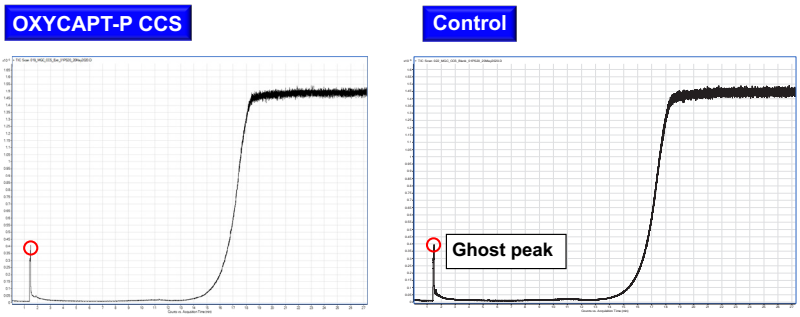


* Quantification was achieved by integration of the LU-UV signals (λ = 220 nm) and using a calibration curve of the external reference BHT.

Figure 7: LC-UV chromatogram of OXYCAPT™ CCS and control with 0.1% aqueous PS-20 solution.

No volatile compound that originates from OXYCAPT™ CCS was detected above AET (0.3 ppm) in 0.1 % aqueous PS-20.

- The chromatogram with OXCAPT™ CCS is almost same with the control.



* Quantification was achieved by integration of the HS-GC-MS TIC signals and using a calibration curve of the external toluene reference.

Figure 8: HS-GC-MS chromatogram of OXYCAPT™ CCS and control with 0.1% aqueous PS-20 solution.

exposure (PDE) as outlined in ICH Q3 (Table 3). Tungsten, which is not listed in ICH Q3D, was not present at a significant level. This result indicates that OXYCAPT™ can contribute to a safety assessment for drugs and the pH stability of drug solution.

CONCLUSION

In addition to the existing data, the latest study results showed that OXYCAPT™ CCS has an excellent resistance to aqueous surfactant, acid, alkali and alcohol solutions. As such, OXYCAPT™ CCS, along with its other well-established benefits, can contribute to the safety and efficiency of biopharmaceuticals and gene and cell therapies owing to its extremely low level of organic extractables and elemental impurities.

ABOUT THE COMPANY

Mitsubishi Gas Chemical is a major chemical products manufacturer operating across a wide range of industries. In the field of drug delivery, the company has developed OXYCAPT™ vial and syringe from a novel polymer, as an alternative to glass primary packaging.

ABOUT THE AUTHORS

Hiroki Hasegawa is a researcher in the Advanced Business Development Division at MGC. He gained a diploma in science in 2013 and a master's degree in science in 2015 from Osaka University (Japan). Since April 2015 he has been working for MGC, in charge of macromolecular science, especially in the composition development of thermosetting resin. Since 2018 he has been part of the team developing multilayer plastic vials and syringes for biologics.

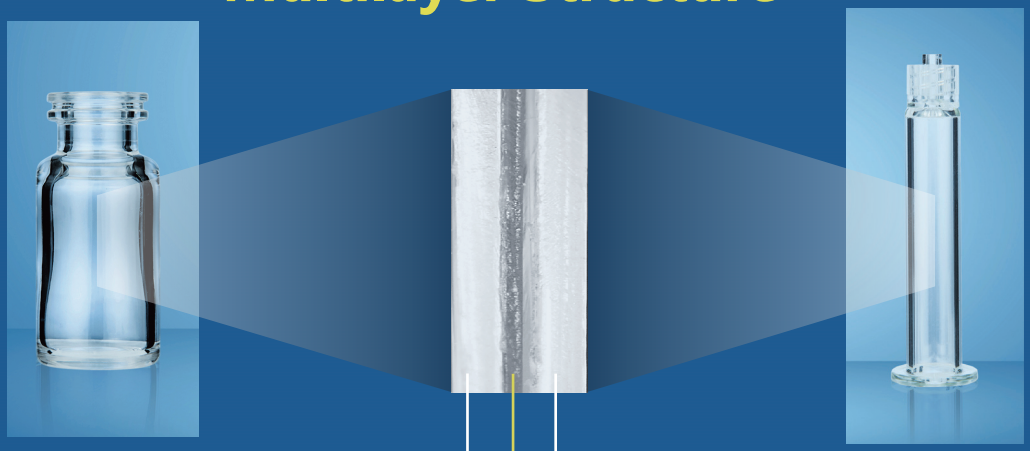
Tomohiro Suzuki joined MGC in 1998. He belonged to the Oxygen Absorbers Division until 2011, after which he was transferred to the Advanced Business Development Division in 2012 to be a member of the OXYCAPT™ development team. Since then, he has been in charge of marketing for OXYCAPT™ vial and syringe.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

Element	0.1% PS-20 solution		pH 3 buffer solution		pH 10 buffer solution		PDE (µg)
	Concentration	Amount administered with 5 syringes (µg)	Concentration	Amount administered with 5 syringes (µg)	Concentration	Amount administered with 5 syringes (µg)	
Ag	< 0.1	< 0.5	< 0.1	< 0.5	< 0.1	< 0.5	10
As	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	15
Au	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	100
Ba	< 0.1	< 0.5	0.1	0.5	0.1	0.5	700
Cd	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	2
Co	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	5
Cr	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	1100
Cu	< 0.1	< 0.5	< 0.1	< 0.5	0.1	0.5	300
Hg	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	3
Ir	< 0.1	< 0.5	< 0.1	< 0.5	< 0.1	< 0.5	10
Li	< 0.01	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	250
Mo	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	1500
Ni	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	20
Os	< 0.1	< 0.5	< 0.1	< 0.5	< 0.1	< 0.5	10
Pb	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	5
Pd	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	10
Pt	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	10
Rh	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	10
Ru	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	10
Sb	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	90
Se	< 0.5	< 2.5	< 0.5	< 2.5	< 0.5	< 2.5	80
Sn	< 0.05	< 0.25	< 0.05	< 0.25	< 0.05	< 0.25	600
Ti	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	8
V	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.05	10
W	< 0.1	< 0.5	< 0.1	< 0.5	< 0.1	< 0.5	n.a.

Table 3: Concentration of each elemental impurity listed in ICH Q3D plus tungsten in a study with ICP-MS.

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Small Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Silicone Oil Free Barrel
- Gamma-sterilized Vial & Syringe
- Customizable
- For Biologics & Gene/Cell Therapy

2, 6, 10, 20mL Vial

Nest & Tub for Vial

1, 2.25mL Syringe

Nest & Tub for Syringe

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