LIGHTHOUSE

THE SCIENCE
OF PHARMACEUTICAL
MANUFACTURING

CASE STUDY

# Achieving Container Closure Integrity During Cryogenic Storage Conditions Using an Optimized Vial Stopper Combination

# Introduction

There has been a sharp increase in the development of innovative therapies in the gene and cell therapy space. Often these therapies require storage at ultracold temperatures as well as an ultracold transport chain for distribution. Investigations over the past decade have shown that these ultracold temperatures pose challenges for the traditional borosilicate glass primary packaging solutions typically used for sterile pharmaceutical product.

In particular, the ultracold temperatures can introduce risk to the container closure integrity (CCI) of stoppered pharmaceutical vials (1), whereby CCI is temporarily lost at the ultracold temperature, but regained when the vial is brought back to room temperature.

More recently, a robust holistic approach for ensuring the CCI of a sterile pharmaceutical vial product needing ultracold storage at -80°C was developed and presented (2). The case study here describes results from ongoing work being done to investigate possible primary packaging solutions for therapies requiring even colder storage temperatures down to cryogenic levels (-150°C to -180°C).

# Cryogenic CCI testing methods

Headspace analysis methods have proven to be the optimum approach for performing CCI testing of deep cold storage product. The methods are deterministic (following USP <1207> terminology), analytical, non-destructive, and have relatively high throughput enabling the analysis of robust statistical sample sets. In addition, methods can be developed and validated for the testing of GMP compliant pharmaceutical product (3). For the work described here, a CCI test method based on the measurement of headspace oxygen depletion was developed.

A cryogenic freezer was used to store samples at temperatures between -150°C and -180°C. The freezer used the gaseous phase of liquid nitrogen to achieve cryogenic temperatures, meaning that a nitrogen-rich environment was created in the sample storage area.

A vial that experiences a CCI failure during the cryogenic storage will therefore ingress nitrogen into the vial headspace through the leak. The ingress of nitrogen results in a reduction of the atmospheric oxygen levels of the original air headspace in the vial. A CCI test method was therefore defined based on the measurement of oxygen depletion to identify a leaking vial.

The data presented in Figure 1 shows the headspace oxygen measured in various types of positive controls after cryogenic storage. The measured oxygen depletions demonstrate that the method can robustly detect leaking vials having gross leak defects (syringe needles through the stoppers) down to laser-drilled micron sized defects.

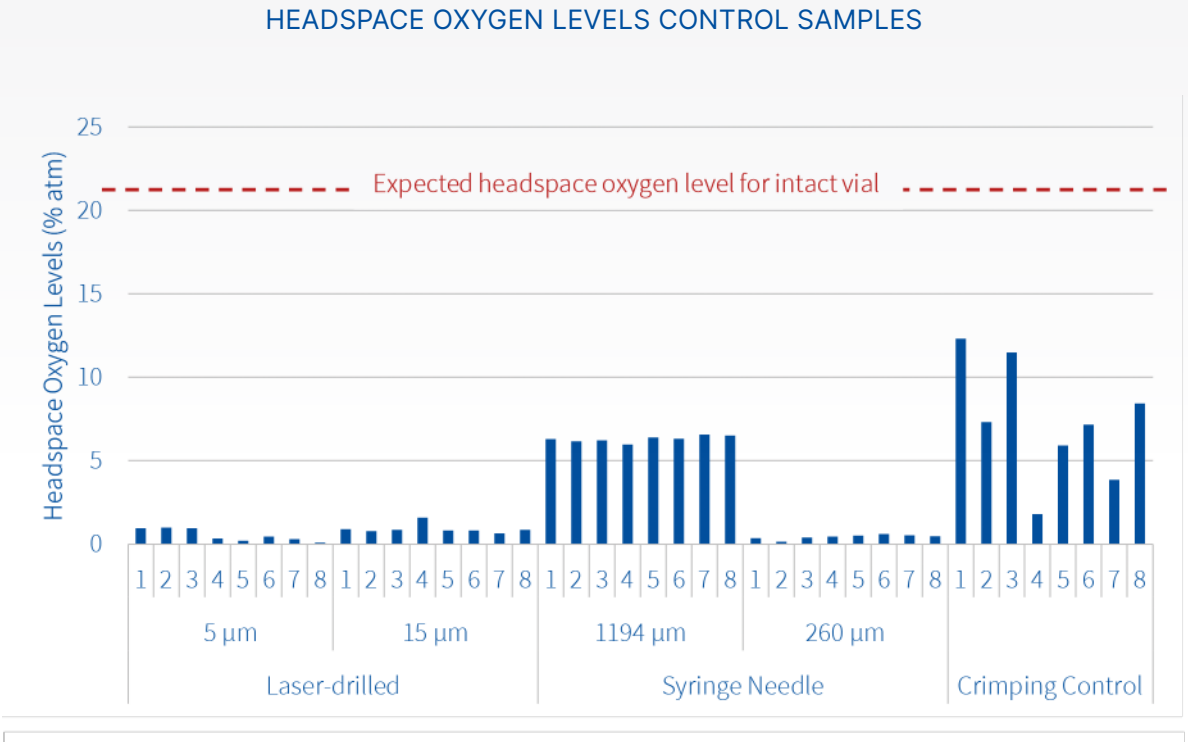


Figure 1: Positive controls in a method development study showing that the measurement of oxygen depletion robustly identified leaking samples after storage in a liquid nitrogen cooled cryogenic freezer.

# Vial-stopper combination CCI study

A specific vial-stopper combination was studied to investigate the sealing performance of the primary packaging components when stored at cryogenic temperatures. The vial used in the study was a 2mL hybrid vial platform from SiO2 Materials Science, which combines a polymer container with a microscopic, glass-like barrier coating system on the inside surface (4).

The rubber stopper used was a readily available chlorobutyl stopper (West 4432). As previous work had shown that the quality of the vial sealing process is critical for deep cold storage product, stoppered vial samples were prepared with different capping pressures to represent samples ranging from loosely capped to tightly capped.

The quality of the vial sealing was determined using residual seal force (RSF) testing, with defined RSF values used to group samples into four sets: low, middle low, middle high, and high capping pressures. In addition, similar sample sets were prepared as control groups using a standard 2R borosilicate glass vial and the same stopper. The samples were then stored in the cryogenic freezer for one week. After removal from cryogenic storage, the samples were measured for headspace oxygen content. The results are shown in Figures 2a and 2b.

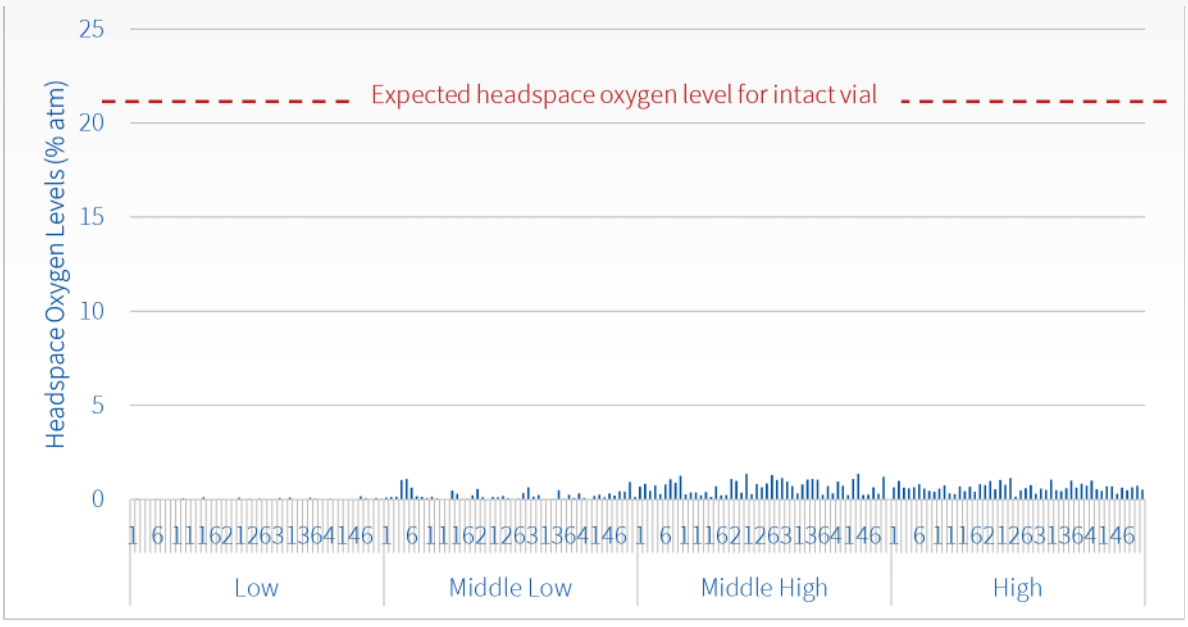


Figure 2a: Measured headspace oxygen levels in the sample control groups consisting of stoppered 2R borosilicate glass vials sealed with a chlorobutyl stopper with four different capping pressures. All samples in all four capping groups show severely depleted oxygen levels, indicating that all samples lost container closure integrity during cryogenic storage, resulting in the ingress of nitrogen displacing the original vial air headspace.

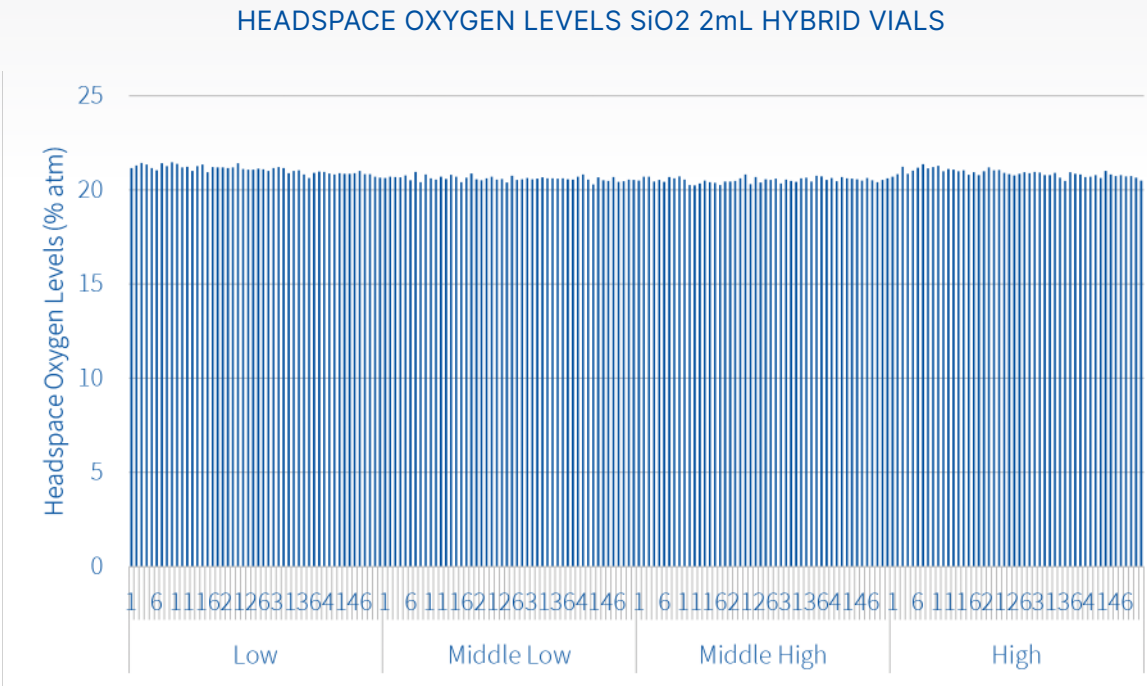


Figure 2b: Measured headspace oxygen levels in the sample groups consisting of stoppered SiO2 2mL hybrid vials sealed with a chlorobutyl stopper with four different capping pressures. All samples in all four capping groups show atmospheric oxygen levels indicating that all samples maintained container closure integrity, and thus maintenance of the original vial air headspace, during cryogenic storage.

# Conclusions

The recent increase in the development of therapies requiring ultracold storage and transport has presented challenges to the traditional pharmaceutical primary packaging solutions.

To bring such therapies to market requires the generation of robust analytical data demonstrating that the primary package is able to maintain CCI at ultracold temperatures. Validation of CCI during the ultracold transport chain is also a requirement.

A prerequisite for the generation of such robust CCI data is the development of an appropriate CCI test method. The laser-based headspace method, such as the one described here, is the only rapid non-destructive analytical technique available for this application as it can measure the temporary CCI failures that occur at these ultracold conditions.

I
n recent years, CCI studies have demonstrated that particular vial-stopper combinations can deliver good CCI performance at temperatures down to -80°C as long as a robust vial sealing process is used.

However, there have been very few examples of stoppered vials delivering acceptable CCI performance at cryogenic temperatures. The results described in this case study show that the SiO2 hybrid vial, when sealed with a standard chlorobutyl stopper, is a promising primary packaging solution for maintaining container closure integrity at temperatures between -150°C and -180°C.

## REFERENCES

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