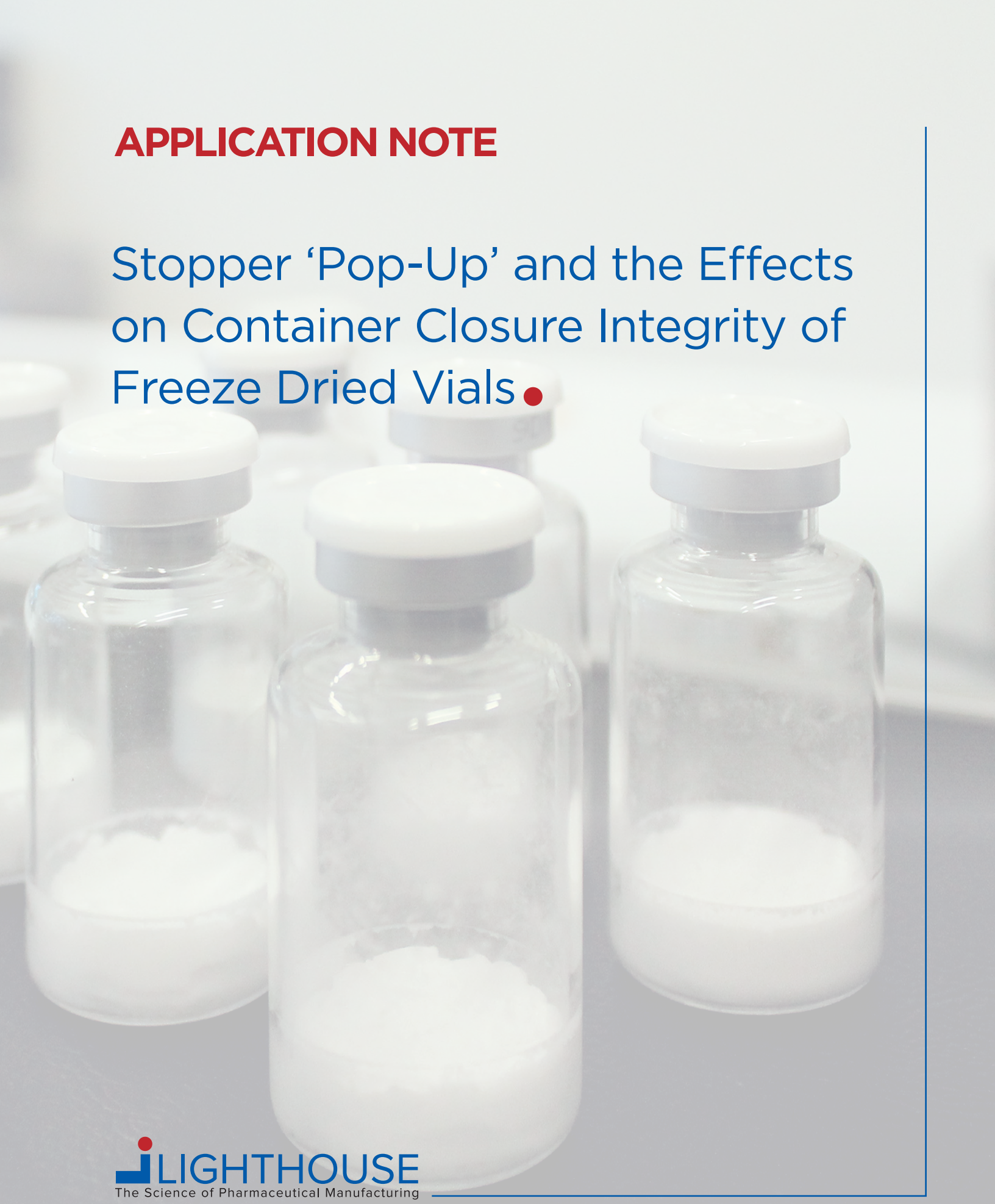
APPLICATION NOTE

Stopper ‘Pop-Up’ and the Effects on Container Closure Integrity of Freeze Dried Vials



LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

INTRODUCTION

Container closure integrity (CCI) plays an important role in maintaining the stability and sterility of lyophilized products. Lyophilization is a complex process that presents many manufacturing challenges one of which is maintaining and monitoring container closure integrity.

At the end of the lyophilization process, prior to sealing finished vials at the end of secondary drying, a lyophilization chamber is typically backfilled to a nitrogen gas pressure that is specified for the vial headspace. The specified headspace pressure varies from product to product. Typically, freeze dried products are stoppered at partial vacuum (0.5 to 0.9 atm of nitrogen pressure) – some products can be sealed under full vacuum (0 atm absolute pressure). The vacuum level serves the practical purpose of helping to seat the stopper and to facilitate reconstitution. Once equilibrium is achieved, the gas pressure in the vial headspace matches the chamber pressure and the shelves are lowered to seat the stoppers into the vial. At this point the vial closure integrity is established but not considered complete until the aluminum seal is applied. Once the shelves are raised, the seal integrity must be maintained for a period of time ranging from minutes to hours to possibly days before unloading and capping occur. It is possible during this time for stoppers to "pop-up" allowing gas ingress into the vial headspace. Stoppers can pop up due to a number of reasons including improper seating during shelf lowering, out of specification stopper and/or vial flange dimensions, and stopper coatings.

If seal integrity is lost during this time period then the physical properties of the headspace (gas pressure and/or composition) will change as gas from the ambient environment outside the vial ingresses into the vial headspace. The practical implications of lost seal integrity are threefold. First, the headspace pressure rises which may impact the ability to reconstitute the product and would likely result in a customer complaint. Second, if the product is oxygen and/or moisture sensitive then the ingress of humid air will result in oxygen and moisture exposure, potentially impacting the product stability. Third, if container closure integrity is breached then sterility can no longer be assured.

METHOD HIGHLIGHTS

Container closure integrity issues due to stopper "pop-up" in the freeze-drying process can be identified and monitored with a CCI testing process. Such a process can either be an automated in-line inspection or a lab-based off-line CCI test. Rapid, nondestructive, laser-based headspace analysis (Figure 1) is a CCI test method technique described in USP <1207>.

Test methods based on the laser headspace technique can verify the closure integrity of each vial by measuring changes in the headspace gas composition or pressure due to a leak. Changes in the gas pressure or gas composition are leak indicators. For vials stoppered under vacuum, a leak causes a rise in headspace pressure towards atmospheric levels.

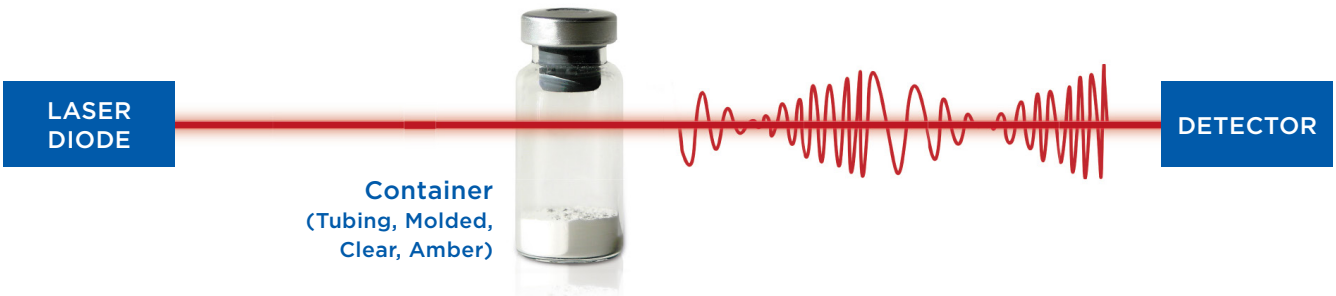


Figure 1: Non-destructive headspace analysis using a laser diode that shines through the headspace of a container. Oxygen, carbon dioxide, moisture, and pressure can be measured in the headspace of parenteral containers.

For vials stoppered at or near atmospheric pressure and exposed to air, a leak causes rising oxygen levels in the vial headspace. The underpressure in freeze-dried vials can drive changes in the headspace composition quickly, even for the case of micro-leaks. Systems that can be used for CCI testing/inspection based on rapid, nondestructive, headspace analysis are shown in Figure 2. Non-destructive headspace gas analysis systems from LIGHTHOUSE are used to monitor container closure integrity for commercial batches of lyophilized product.

Figures 3 and 4 show data from an investigation that was performed to determine the container closure integrity of oxygen sensitive lyophilized product, stoppered with a nitrogen headspace near atmospheric pressure (0.8 atm of nitrogen). A number of vials from a commercial batch showed elevated levels of oxygen during routine QC analysis using a destructive oxygen analysis method. It was therefore decided to test the entire batch using nondestructive headspace oxygen analysis. A 100% inspection of the batch revealed elevated oxygen levels in samples located at specific positions in the freeze dryer due to stopper pop-up issues.

Figure 2: The LIGHTHOUSE Headspace Inspection Systems. Left: Benchtop Analyzer, Right: PULSAR Automated machine.

BENEFITS

- Laser-based headspace is analytical and rapid
- Valuable product is not destroyed
- Measurement method is robust and independent of operator
- Scalable for 100% product inspection
- Enables efficient, accurate qualification, optimization and validation of product lines
- The robustness and easy operation of the platforms allow for at-line or automated in-line implementation in the production environment

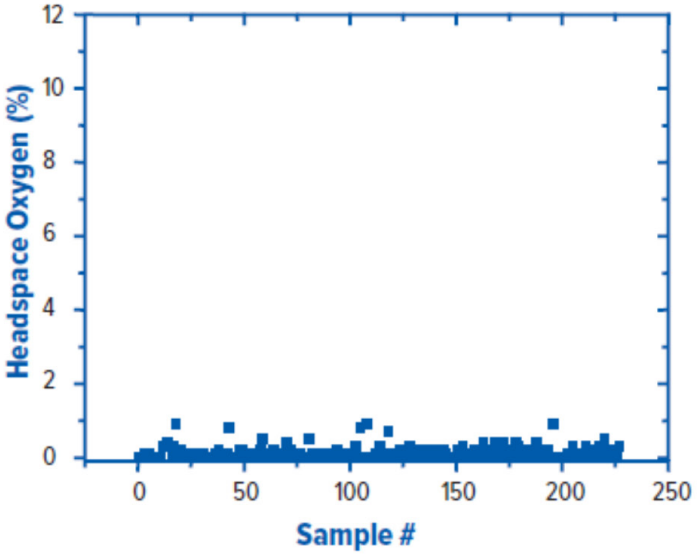


Figure 3: Headspace oxygen content of vials located in zones 4-6. Vials from this location in the freeze dryer showed no evidence of stopper pop up.

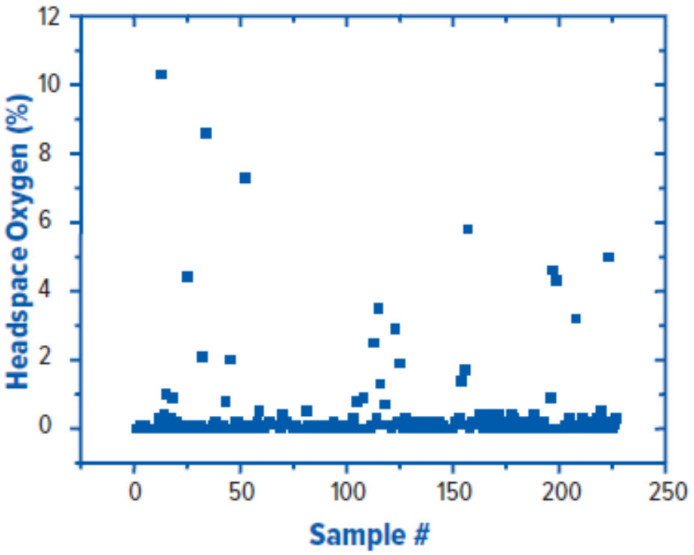


Figure 4: Headspace oxygen content of vials located in zones 1-3. Vials in these locations show air ingress due to stopper pop-up.

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