# Case Study: Container Closure Considerations for Coated Stoppers

LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

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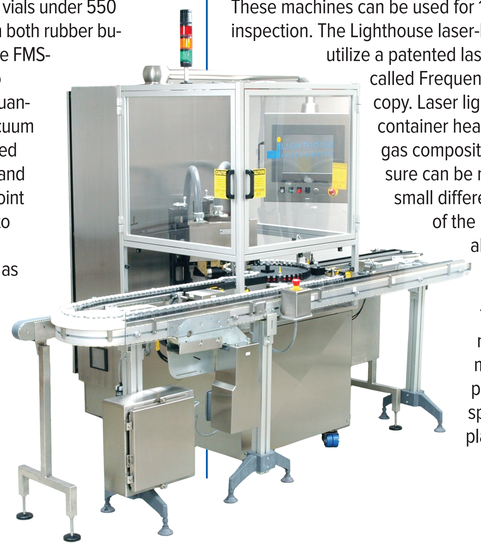
## Introduction

The use of coated stoppers for sealing product vials containing high potency/concentration biotech drug product has increased over the past few years. Stoppers provide a barrier between rubber stopper and the drug formulation. This barrier protects against interaction between the drug and extractables and leachables that can be found in rubber stoppers. The use of coated stoppers requires special attention to container closure integrity. The protective rubber stopper surface can drastically change the sealing properties due to the relatively small sealing surface available to the vial. Well-designed container studies should be carried out to ensure that the vial/stopper combination and stoppering, capping, & crimping processes are robust enough to ensure good consistent sealing integrity.

## Method

A potential container closure issue was identified in demonstration batches of a lyophilized product. The lyophilized product was packaged in 10 ml vials under 550 mbar of nitrogen and stoppered with both rubber butyl and coated stoppers. A Lighthouse FMS-1400 benchtop analyzer was used to perform vacuum leak detection by quantitatively determining headspace vacuum levels. Product samples were analyzed as a function of shelf, shelf position, and as a function of stopper type to pinpoint the container closure issue. Parallel to this troubleshooting activity, a Lighthouse VISTA system was configured as an in-line 100% inspection machine. The VISTA machine simultaneously inspects headspace oxygen, vacuum, and moisture levels of the lyo product at production speeds.

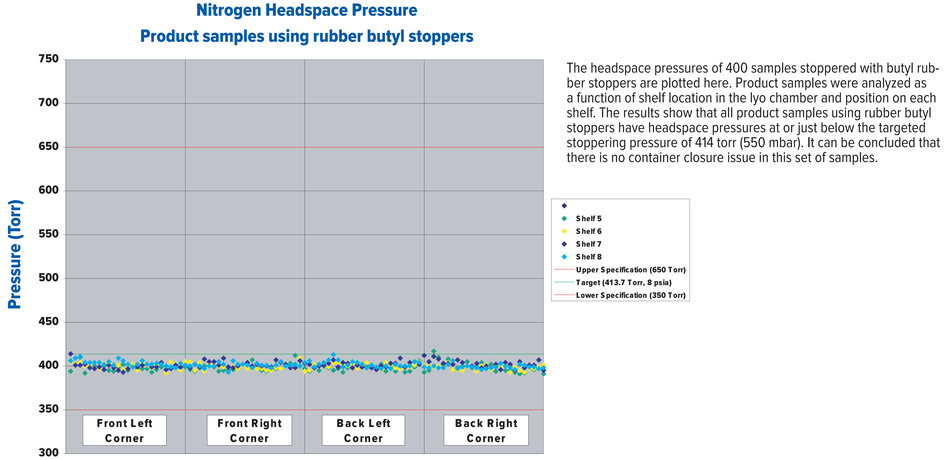


## Platforms

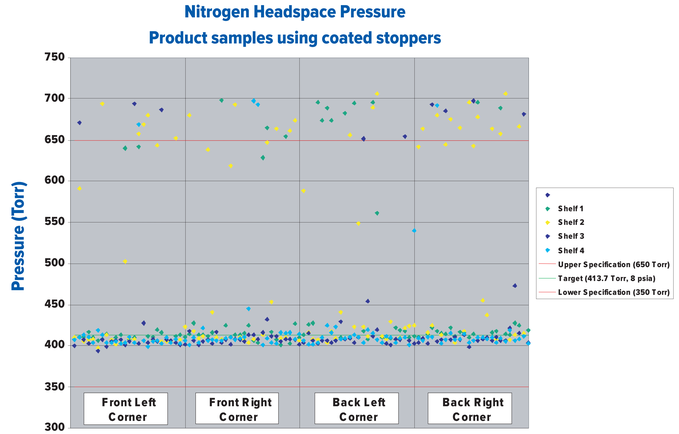
A Lighthouse FMS-1400 Analyzer was used to perform rapid non-destructive headspace vacuum leak detection of the freeze-dried product vials.

A Lighthouse VISTA/THC™ machine was configured as an in-line 100% inspection machine. The VISTA machine was configured to simultaneously inspect headspace oxygen, vacuum, and moisture levels of the lyo product at production speeds. These machines can be used for 100% container closure inspection. The Lighthouse laser-based sensor platforms utilize a patented laser measurement method called Frequency Modulation Spectroscopy. Laser light is directed through the container headspace. The headspace gas composition and stoppering pressure can be measured by monitoring small differences in the transmission of the laser when tuned to an absorption line of the water or oxygen molecule and modulated in frequency. The rapid non-destructive nature of the measurement makes the VISTA platform an ideal 100% inspection or PAT monitoring platform.

## Results




The headspace pressures of 400 samples stoppered with butyl rubber stoppers are plotted here. Product samples were analyzed as a function of shelf location in the lyo chamber and position on each shelf. The results show that all product samples using rubber butyl stoppers have headspace pressures at or just below the targeted stoppering pressure of 414 torr (550 mbar). It can be concluded that there is no container closure issue in this set of samples.




The headspace pressures of 400 samples using coated stoppers are plotted here. Product samples were analyzed as a function of shelf location in the lyo chamber and position on each shelf. The results show a significant number of samples having headspace pressures well above the targeted stoppering pressure of 414 torr (550 mbar). These results indicate a container closure issue for this set of product samples. Because leaking vials were detected independent of location in the lyo chamber, it can be concluded that the sealing issues are a result of an issue with the vial / stopper combination.

## Conclusion

Troubleshooting a suspected container closure issue for a lyophilized product stoppered under 550 mbar of nitrogen revealed an issue with the vial / stopper combination. Specifically, the issue was related to the use of a coated stopper. Container closure failure rates of approximately 20% were detected through non-destructive headspace vacuum leak detection. The solution to this issue came from the coated stopper supplier who suggested venting the lyo chamber to 1 atmosphere of nitrogen BEFORE raising the shelves instead of after raising the shelves. Further vacuum leak detection studies confirmed that this process change lowered the container closure failure rate to within the range 0.5 - 1.0%. Following this process change, an in-line Lighthouse VISTA inspection machine was implemented to detect and reject the residual container closure failures. Leaking vials are detected by monitoring headspace vacuum and oxygen levels and are rejected based on a user defined reject limit.