Raised Stopper Detection in Freeze Dried Vials – Visual Inspection versus Headspace Inspection

LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

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Introduction

There is a drive in the industry to implement inspection systems that help ensure the seal integrity of finished product vials. This includes vision sensor systems for 100% automatic detection of raised stoppers on vials containing lyophilized drug products prior to capping and sealing. A second type of inspection system which is increasingly being implemented is laser-based machines for 100% headspace inspection. This Poster describes how laser-based headspace inspection detects vials having raised stopper issues. Results from detailed laboratory studies investigating raised stopper behavior during the lyophilization process conclude that raised stopper height and vial leakage do not directly correlate but are rather described by a probability function. Even more interesting, it is shown that the process steps at the end of secondary drying can be designed in such a way so as to minimize the probability of vial leakage as a function of raised stopper height. Data from a 'raised stopper vials' industry case study is presented showing how quantifying the physical headspace conditions also enables science-based process troubleshooting and optimization.

Leak Probability as a Function of Stopper Height

Studies were performed using 10ml clear tubing vials, grey siliconized lyo stoppers, and a Lyostat 1 pilot freeze dryer. Empty vials were prepared using plastic shims between the sealing surfaces of the vial and the stopper. The shims were of different thicknesses (0.5, 1.0, 1.5, and 2.0 mm) so that when the vials were closed at the end of the lyo cycle, samples at different defined raised stopper heights were produced. The objectives of the studies were threefold:

- Investigate leak probability as a function of raised stopper height
- Investigate leak probability as a function of headspace vacuum level
- Investigate leak probability as a function of stoppering at the end of the lyo cycle

After being loaded into the Lyostat 1 freeze dryer, the empty vials were evacuated, back filled to a defined nitrogen pressure and stoppered, and the chamber vented with air to remove the vials for further study. Different runs were used to produce vial samples at headspace pressures of 0, 250, 500, and 750 mbar of nitrogen. In addition, two different stoppering processes were used: a) 'close and release' involved lowering the shelves to stopper the vials and then raising them before venting the lyo chamber to atmosphere, b) 'close and hold' involved lowering the shelves to stopper the vials and holding them in the lowered position until after the chamber had been vented to atmosphere. After one hour in an uncapped condition, the vials were analyzed with LIGHTHOUSE Headspace Oxygen and Pressure Analyzers to determine the headspace oxygen and pressure levels. Headspace conditions that were different than the specified conditions at stoppering identified vials that had or were in the process of leaking.

Results Raised Stopper Study

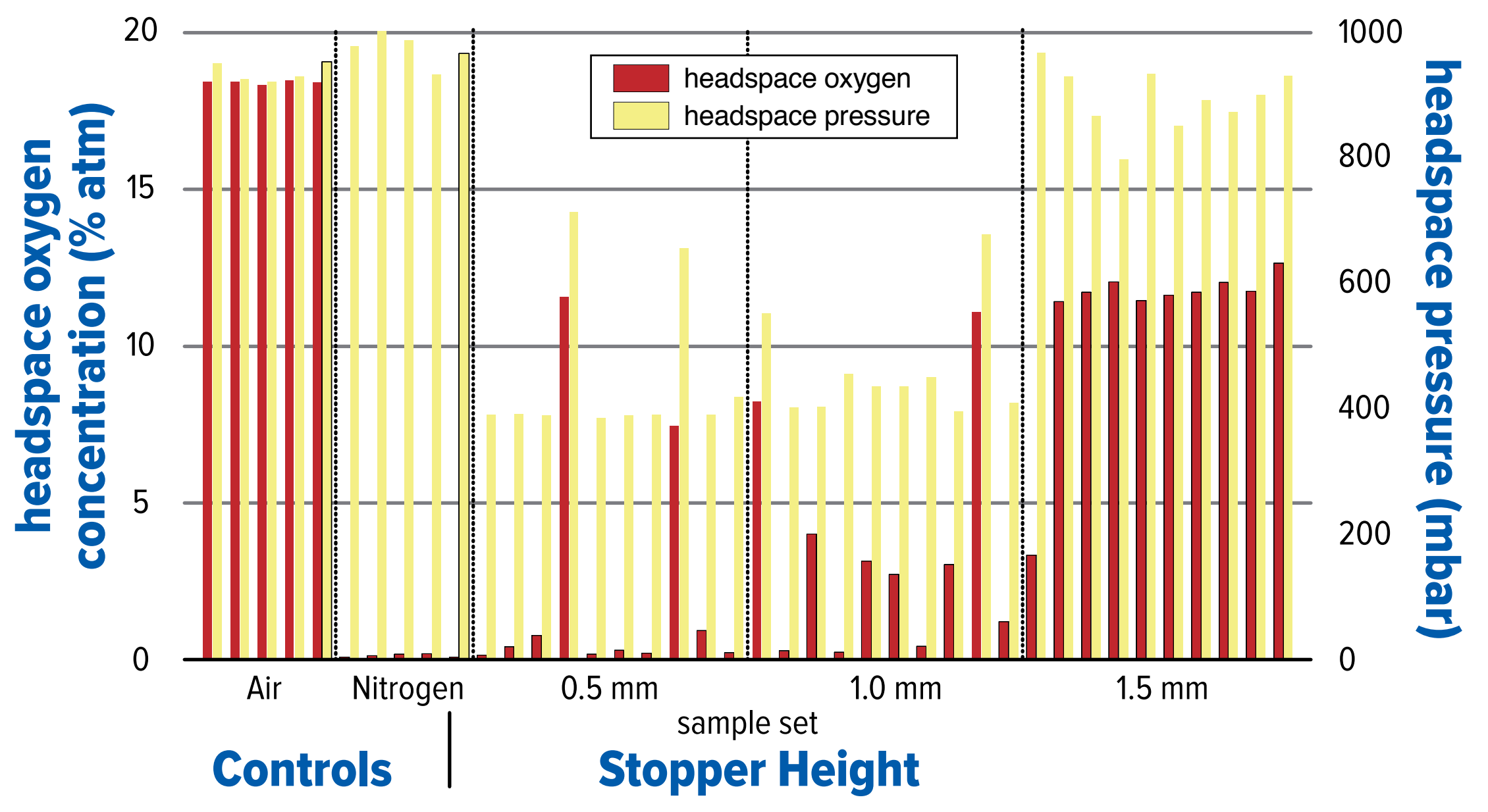

Figure 2. Headspace oxygen and headspace pressure data from a raised stopper experiment. Also plotted are sets of air and nitrogen control vials. The data is an example of how physical characterization of the headspace gas composition gives insight into the container closure integrity of lyo vials.

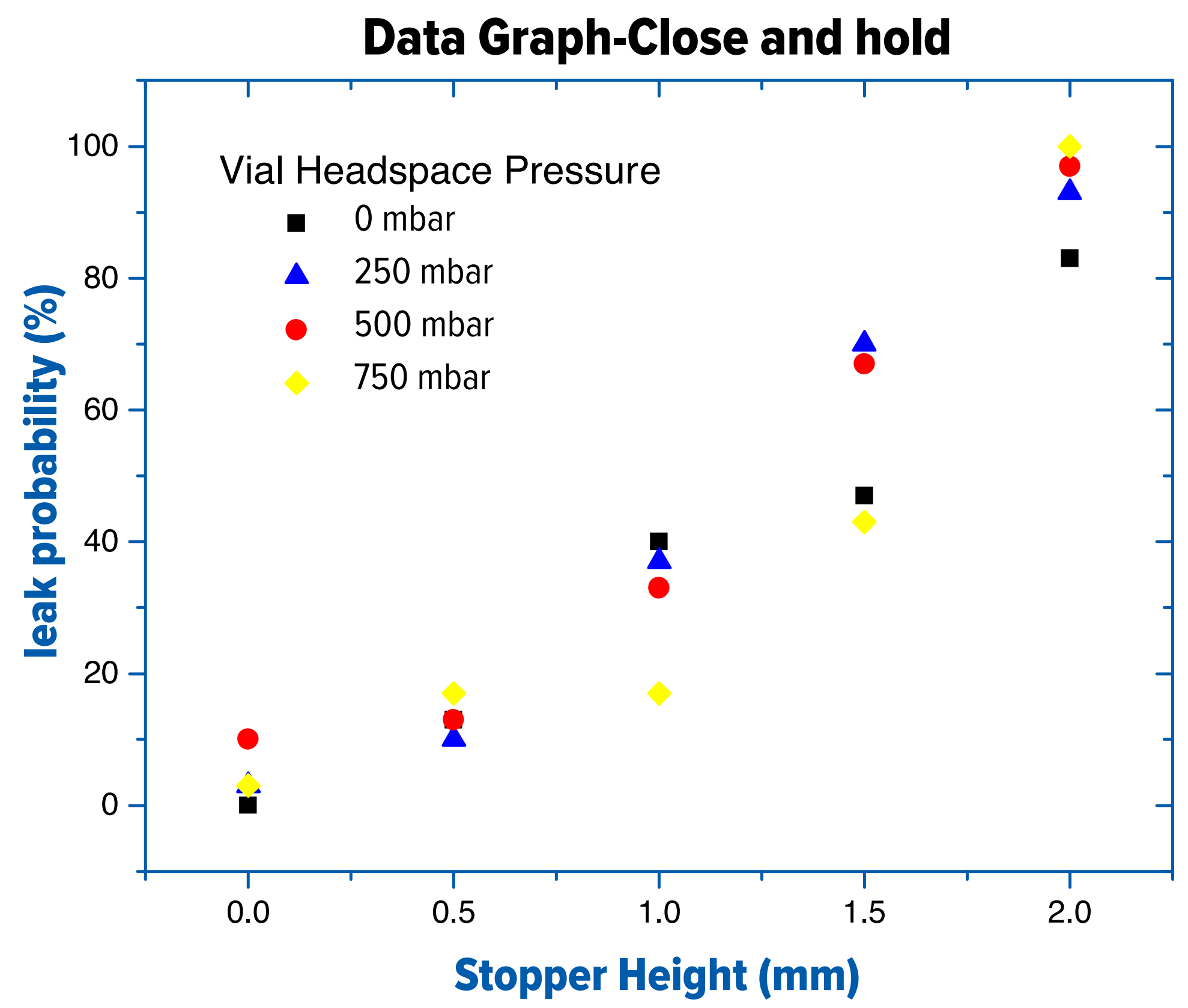

Figure 4. Leak probability as a function of raised stopper height and as a function of different headspace pressures. The results show that the leak probability does not depend on the initial headspace pressure. The results in this graph come from samples stoppered with the 'close and hold' process. Compared to the results of the 'close and release' samples in Figure 3, one sees that the 'close and hold' process significantly lowers the probability of leaks due to raised stoppers.

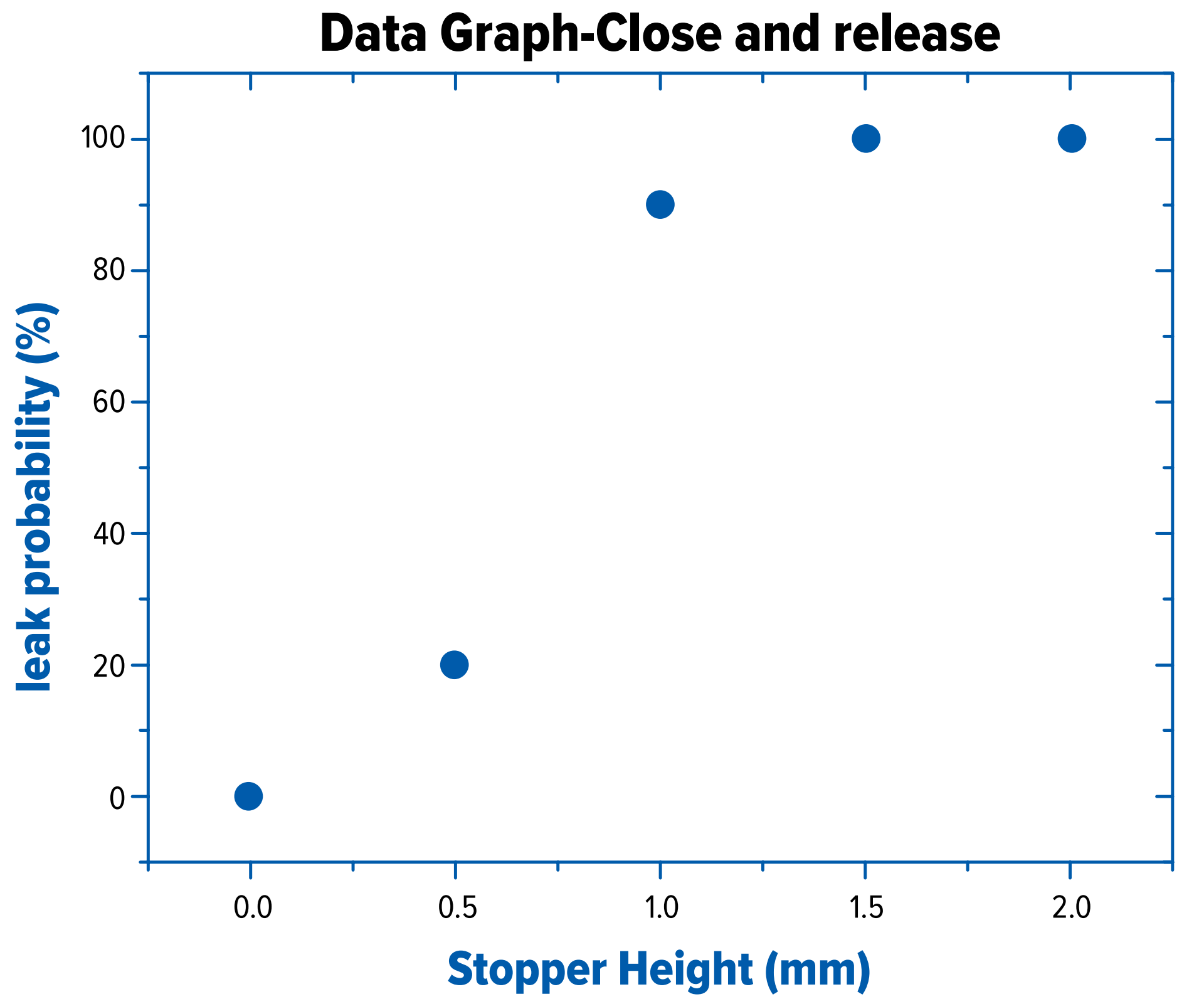

Figure 3. Plot of leak probability as a function of stopper height for lyo vials stoppered with the 'close and release' process.

Industry Case Study

Here we describe an industry raised stopper case study involving a commercial batch of lyophilized product. The batch consisted of approximately 11,000 vials stoppered at 600 mbar of nitrogen. A suspected raised stopper issue motivated the manufacturer to perform 100% laser-based headspace inspection of the batch a few weeks after production. Some of the raw data is shown in Figures 5 & 6.

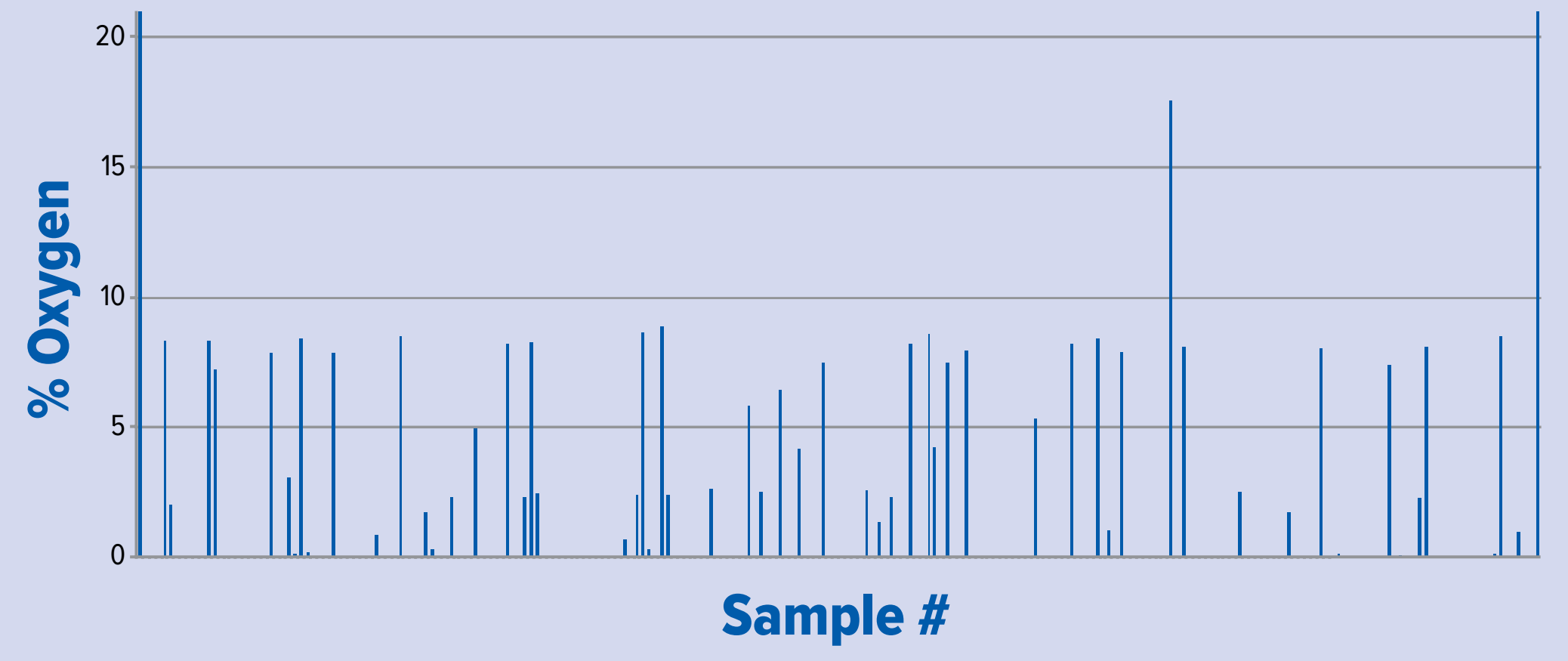

Figure 5. Headspace oxygen results for a subset of the product samples measured in a commercial lyo batch. It is clear from these results that a significant percentage (~ 25%) of the product vials has high oxygen content, presumably due to leaks that ingress air into the headspace. It is interesting to note that a large proportion of the high oxygen product samples have oxygen levels around 8% and that only one product sample contains near atmospheric oxygen levels.

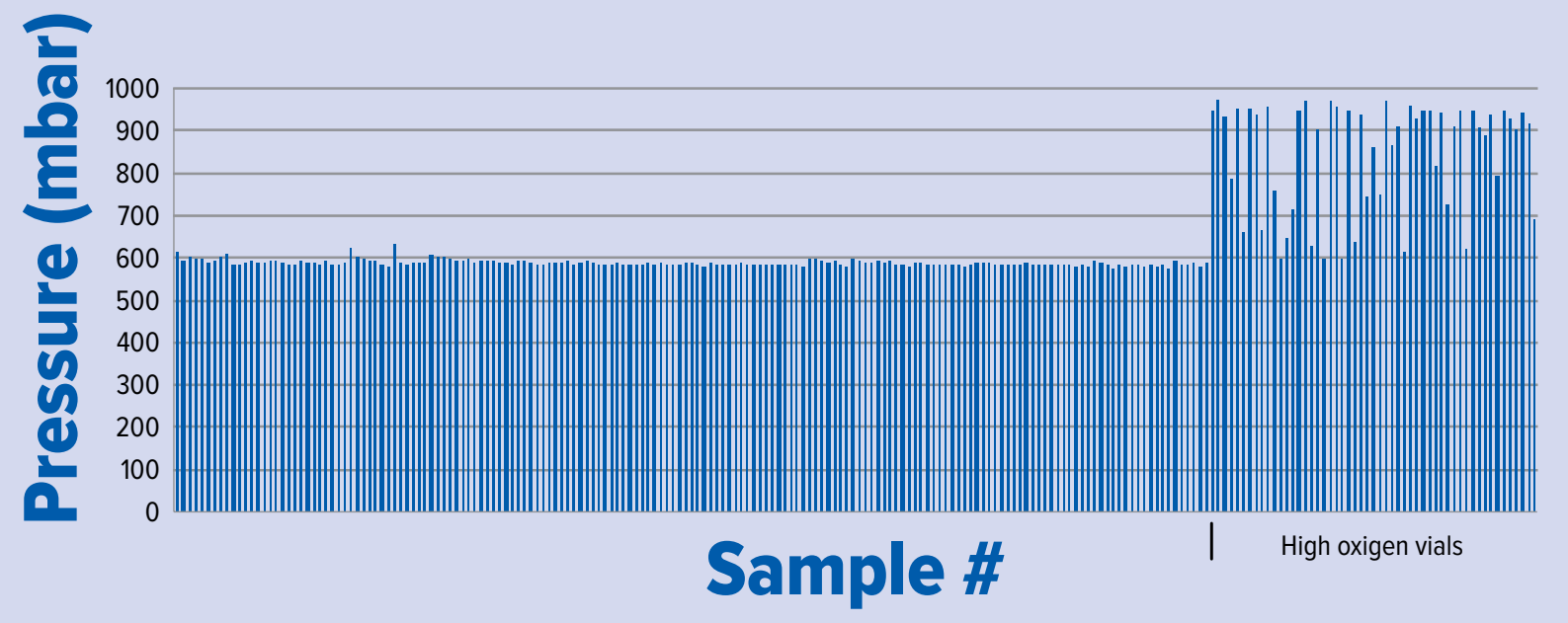

Figure 6. The measured headspace pressures give additional insight into the container closure issues in the batch. The headspace pressures of the high oxygen content vials are plotted on the righthand side of the plot. It is now clear that the high oxygen content vials have lost vacuum relative to the specified stoppering pressure of 600 mbar with a large proportion of the defective vials showing headspace pressures near one atmosphere

In Figure 7, analysis of the headspace inspection data identifies three categories of leaking vials:

Category 1 – Temporary gross leaker: It can be seen that vials having 8% headspace oxygen levels have headspace pressures near one atmosphere. Raised stoppers in these vials resulted in gross leaks from the freeze dryer to the capping machine causing 400 mbar of air (corresponding to 8% oxygen) to quickly ingress into the product vials. The capping process stopped the leaks sealing these vials under headspace conditions of 8% oxygen and one atmosphere.

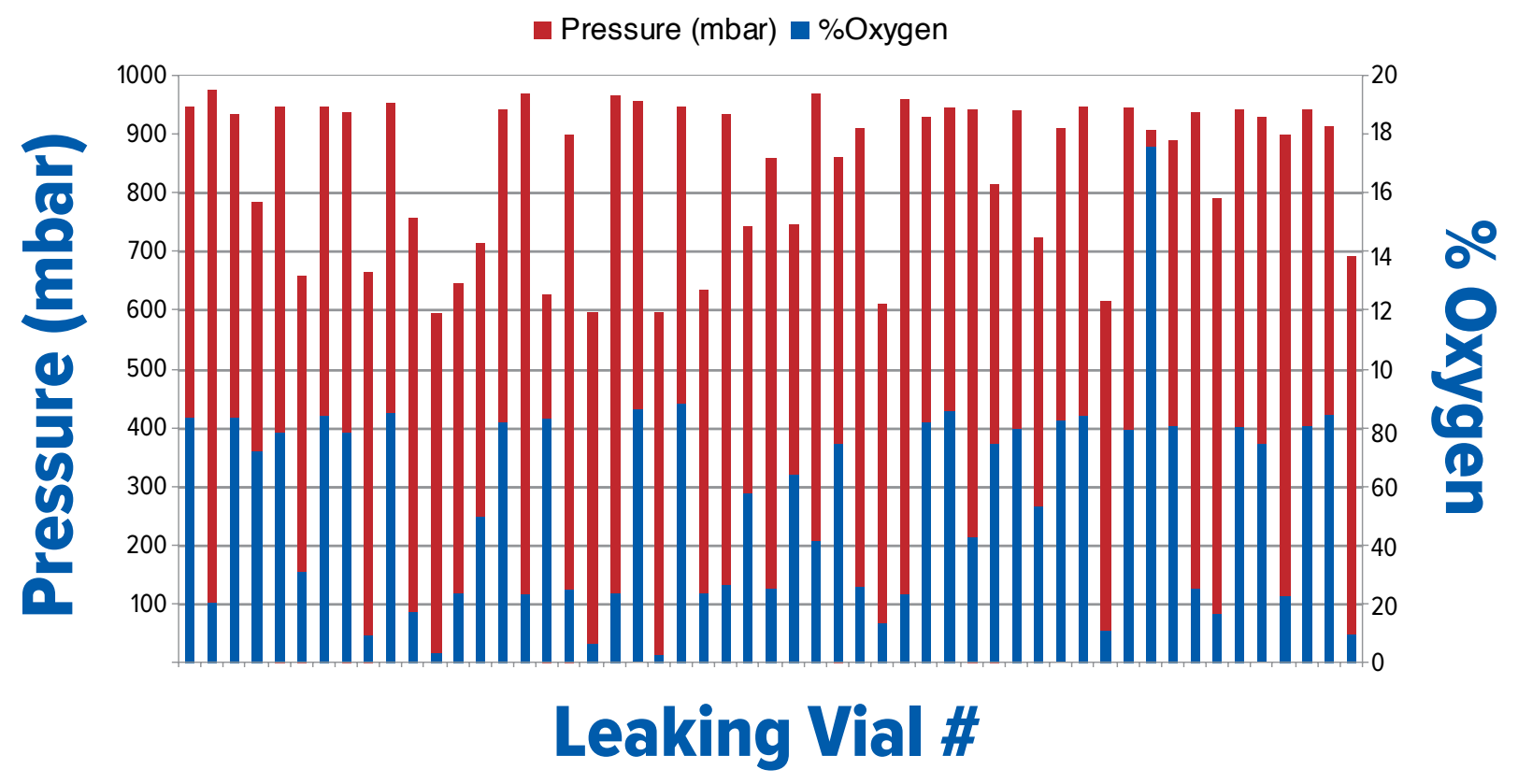

Figure 7. The correlation between the headspace oxygen and headspace pressure measurements in the defective vials is plotted in this Figure and provides the deepest insight into the closure integrity issue of this particular batch.

Category 2 – Permanent leaker: One vial in Figure 7 can be seen to have near atmospheric oxygen and pressure levels. This vial also had a raised stopper coming out of the freeze dryer resulting in a leak. In contrast to the vials described in Category 1, the capping process did NOT stop the leak. After an initial ingress of 400 mbar of air into the headspace driven by the pressure differential inside and outside of the vial, this vial continued to ingress air after capping through diffusion resulting in atmospheric oxygen levels.

Category 3 – Temporary partial leaker: The remaining defective vials have oxygen levels between 0.5% up to 8% and headspace pressures between 600 mbar up to one atm. The raised stoppers in these vials resulted in smaller leaks. Between the freeze dryer and the capping machine, these vials ingressed some amount of air partially raising the headspace pressures above 600 mbar. Capping then sealed the vials under a range of partially elevated headspace oxygen and pressure levels.

Conclusions

Two conclusions can be drawn from the raised stopper studies presented in this poster. First, the closure failure rate is a probabilistic function of the stopper height. Although vision sensors can be used to determine stopper height, correlating stopper height to a leak in a sterile vial can be problematic. Setting a non-zero stopper height as a reject limit before capping will result in the rejection of good vials and, more problematic, possible acceptance of bad vials. Second, headspace inspection provides a direct measure of container closure integrity by detecting physical changes in the headspace conditions of a leaking freeze dried vial. The industry case study shows how headspace inspection not only detects leaking vials in a commercial lyo batch, but also how headspace inspection can give detailed insight into the origin of the container closure issues. Implementation of 100% headspace inspection after capping enables detection of all vials that have leaked, even when the leak was transient to some point in the manufacturing process. It should be noted that headspace inspection will detect not only leaks due to raised stoppers, but also leaks due to cracks in the vial, defects under the aluminum seal, out-of-specification vials/stoppers, etc.