LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

Technical Note 205

Sterile production process studies using 100% headspace inspection of finished product

INTRODUCTION

Recent regulatory guidance on process validation and the implementation of Quality by Design (QbD) principles in the pharmaceutical industry has emphasized product and process understanding and process control, based on sound science and quality risk management. The analysis of statistical sets of finished pharmaceutical product is increasingly being used to determine if the process is capable of reproducible commercial manufacturing. An assessment can then be made if the risk in the commercial manufacturing process merits 100% inspection of finished product. The Lighthouse PULSAR Headspace Inspection System is an automated 100% inspection platform designed to measure the physical headspace conditions in sealed parenteral containers. The measurements are based on spectroscopic methods and are analytical, rapid, and non-destructive. This Technical Note describes the application of the PULSAR inspection platform to perform 100% headspace oxygen monitoring during the filling of oxygen-sensitive formulations, 100% container closure inspection of suspect batches, moisture inspection of freeze dried product, and automated media fill inspection.

Sterile production process studies using 100% headspace inspection of finished product

Application 1: Headspace oxygen monitoring

Sterile liquid filling lines are increasingly being implemented with nitrogen purge capability during filling. Large molecule biopharmaceuticals can be prone to oxidation and to prevent this from occurring, the headspace is often purged with an inert gas during filling to ensure a longer shelf life. Figure 1 shows the measured headspace oxygen in syringes filled and purged on a line being qualified in a new parenteral manufacturing facility. An initial series of syringes analyzed at-line showed some samples having oxygen levels above the 5% specification. After optimization of the filling process, a later series showed syringes being produced with no outliers. Process studies that perform 100% batch inspection give insight into the robustness of the process. The implementation of 100% monitoring in commercial manufacturing guarantees the quality of finished product.

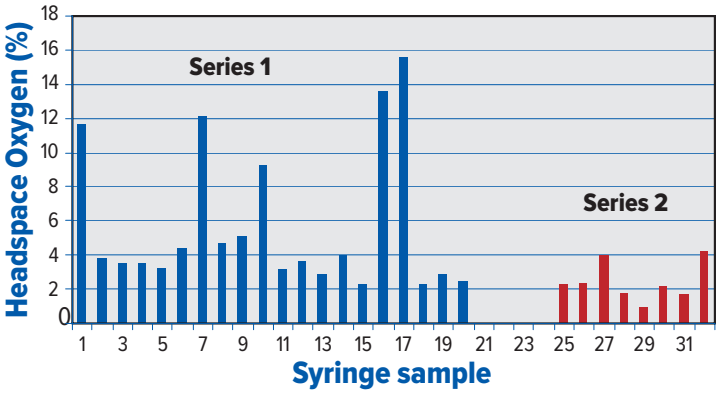

Figure 1: Measured headspace oxygen in syringes filled on a line being validated in a new manufacturing facility. An initial series showed some syringes having headspace oxygen levels above the 5% specification. The optimized process produced syringes with no outliers.

Application 2: 100% container closure inspection

Container closure integrity (CCI) plays an important role in maintaining the sterility and stability of sterile pharmaceutical products. Concerns over patient safety, customer complaints, and the cost of investigations and product recalls have recently resulted in revised regulatory guidance in this area. Manufacturers of sterile product have taken advantage of the availability of lease headspace inspection machines to implement 100% CCI inspection of product batches having suspected CCI issues. Figure 2 shows the inspection results from a batch of freeze dried product where a

raised stopper issue was identified resulting in a risk to CCI. Each batch consisted of approximately 30,000 vials stoppered at 0.2 atm of nitrogen. A lease headspace inspection machine was configured to measure headspace oxygen levels with a leaking vial identified by elevated oxygen levels resulting from air ingress through the leak. The project timeline resulted in a fully qualified inspection machine installed and ready to begin product inspection by week 12. Approximately 3% of the batch of 30,000 vials in Figure 2 was identified to have headspace oxygen levels above the defined oxygen limit. These vials could be rejected and good product released to the market.

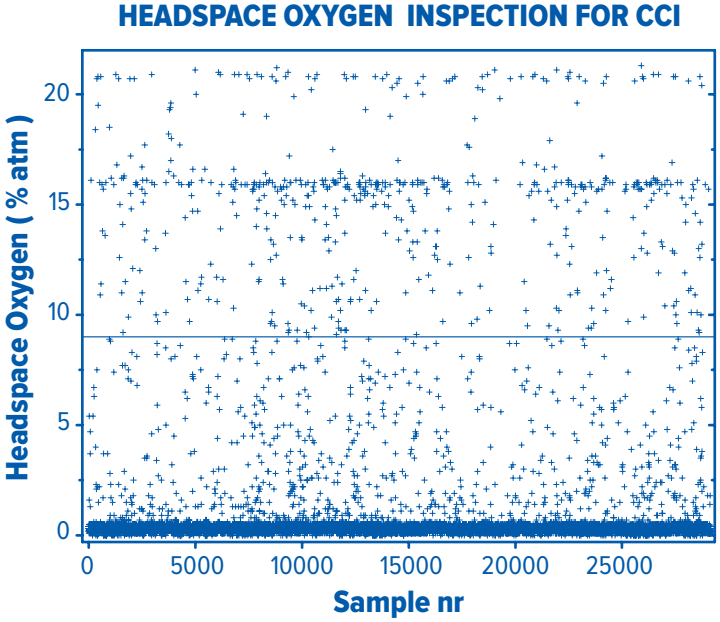

Figure 2: Measured headspace oxygen levels in a commercial batch of lyo product. The results identified a raised stopper issue and allowed the client to reject bad vials and ensure container closure quality of the remaining product vials.

Application 3: Freeze dryer moisture mapping

The traditional methods for residual moisture determination in the pharmaceutical industry are Karl Fischer (KF) titration methods. For process studies, these methods are not conducive to conducting studies with statistically relevant sample sets as they are resource intensive and sample analysis throughput is limited. Moreover, valuable product is destroyed because of the destructive nature of the measurement. The absence of statistically relevant data means that residual moisture studies are at risk of being imprecise and that limited insight can be gained into the consequence of process variability on final product quality. Headspace water vapor levels measured inside of a freeze-dried vial have been directly correlated to KF measurements of those same vials. Figure 3 shows the measured headspace moisture levels of freeze-dried product produced on a shelf in a pilot freeze dryer. The numbers in the graphic are the measured water vapor levels in each vial in units of torr with the darker colors

representing higher moisture values. Tracking the location of the vials on the lyo chamber shelf enables generation of a moisture map that clearly shows a wet spot in the middle of the shelf. Using an inspection platform for 100% headspace moisture analysis of lyo product batches gives full insight into final product quality variability, which in turn enables efficient cycle development and optimization and freeze dryer qualification. The implementation of 100% inspection in commercial manufacturing guarantees the quality of finished product.

Application 4: Automated media fill inspection

Opportunities for improving and streamlining the media fill process are interesting for aseptic filling operations. In particular, the manual visual inspection process used to inspect media vials for signs of contamination after incubation is considered to be tedious and time-consuming. Because the visual inspection is performed by operators, there is also risk for human error due to subjectivity and fatigue. In addition, difficult-to-inspect containers such as molded or colored glass, or certain plastic containers, pose inspection challenges for operators. An inspection method that is analytical and automated should improve the media fill inspection and fit with the industry trend of removing human subjectivity from the process. Studies have demonstrated that laser-based headspace inspection platforms can detect microbial growth in media-filled pharmaceutical containers. For detecting microbial growth, the levels of headspace oxygen and carbon

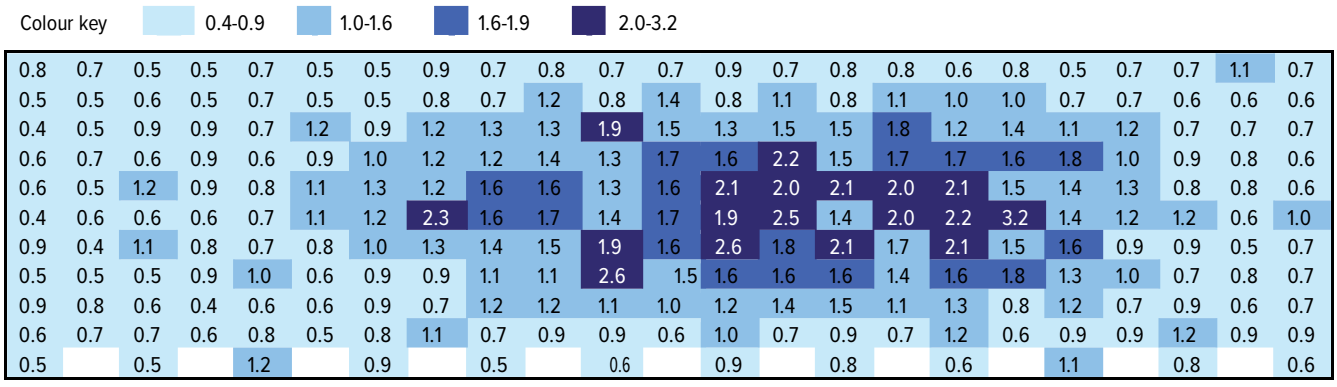

Figure 3: Moisture map showing a wet spot in the center of the freeze dryer shelf.

dioxide are measured in the media vials. Figure 4 shows that once aerobic microorganisms begin to grow, there will be a significant consumption of oxygen in the sealed container as well as a corresponding production of carbon dioxide. The implementation of a 100% headspace inspection machine enables an automated analytical media fill inspection process that has advantages over current manual visual inspection methods.

BENEFITS HEADSPACE PROCESS STUDIES

- Analysis of statistical sample sets
- Deep insight into finished product quality and process variability
- Non-destructive measurement saves valuable product
- 100% batch inspection enabled to guarantee finished product quality
- Variety of critical product attributes (CCI, residual moisture, headspace oxygen) can be monitored

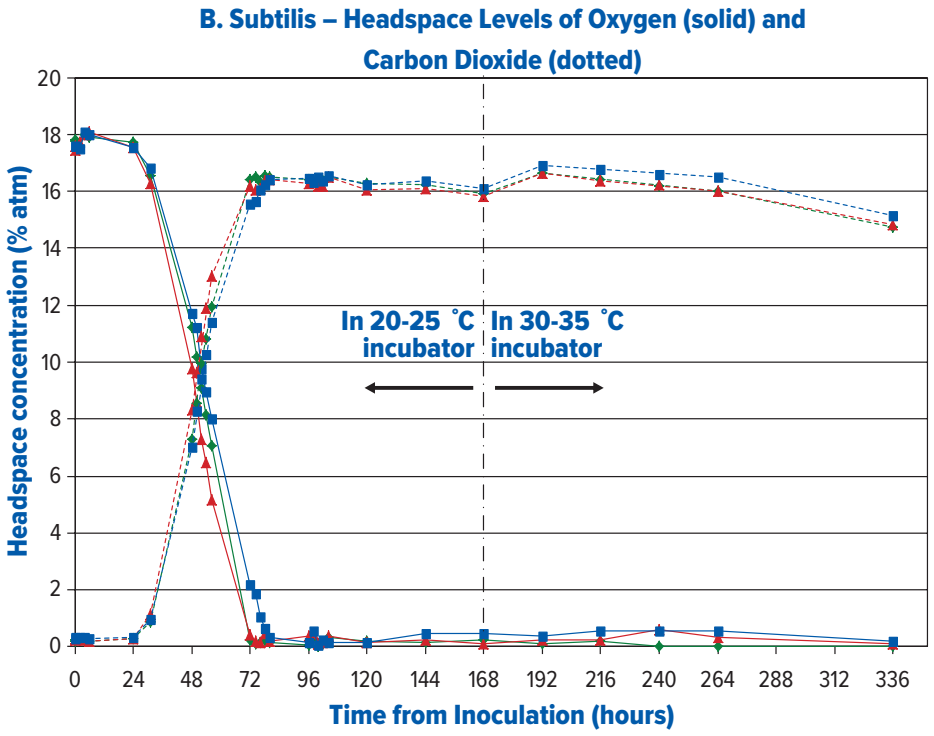

Figure 4: Headspace oxygen and carbon dioxide concentrations in three media vial samples injected with < 100 CFU of Bacillus subtilis (ATCC 6633) plotted over the 14 day incubation period. Growth is detected after 24 hrs with the headspace conditions changing drastically in the first 72 hrs.