LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

Customer note **101**

Case Study: 100% Container Closure Inspection of Freeze Dried Drug Product in Quarantine

Introduction

Lyophilization is a complex process that presents many manufacturing challenges, one of which is maintaining and monitoring container closure integrity of the finished package. Container closure integrity plays an important role in maintaining the sterility and stability of lyophilized products. Concerns over patient safety, customer complaints, and the cost of investigations and product recalls have recently resulted in revised regulatory guidance (e.g. the revised Annex 1 of the European Guidelines for the Manufacture of Sterile Products).

Industry Case Study

A leading contract manufacturer approached LIGHTHOUSE with a concern about the container closure integrity of vials in several commercial batches of lyophilized product. Each batch consisted of approximately 30,000 vials stoppered at 200 mbar of

Case Study: 100% Container Closure Inspection of Freeze Dried Drug Product in Quarantine

nitrogen. A suspected raised stopper issue motivated the manufacturer to place several batches into quarantine and a decision was made to perform 100% container closure inspection of the product vials.

To identify all potentially leaking vials, the manufacturer asked LIGHTHOUSE to configure a headspace inspection machine for automated 100% container closure inspection. The machine was configured with a headspace oxygen sensor to measure the headspace oxygen levels in every vial. A leaking vial would be identified by elevated oxygen levels resulting from oxygen ingress through the leak. Due to the critical timeline, a standalone lease machine was configured for fast delivery. The timeline was for Factory Acceptance Testing to be performed eight weeks after the project start, the IQ/OQ in week 9, and the PQ in weeks 10 and 11 so that inspection of product could begin in week 12.

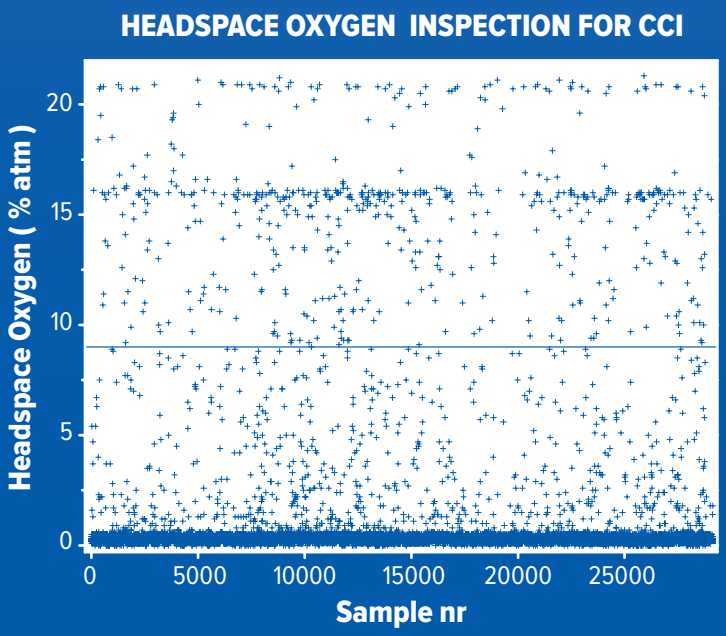

Figure 1: Measured headspace oxygen levels in a commercial batch of lyo product. The results identified a raised stopper issue and allowed the client to reject bad vials and ensure container closure quality of the remaining product vials.

Figure 1 shows the inspection results from a batch where a raised stopper issue was indeed identified. Approximately 3% of the 30,000 vials were identified to have headspace oxygen levels above the defined reject level of 9% oxygen. The inspection process identified gross leakers as well as vials that had temporarily leaked.

Conclusions

Container closure integrity has become an increasingly important topic for the quality assurance of sterile freeze-dried product. Today, many of our clients have implemented, validated, and registered automated LIGHTHOUSE inspection machines for 100% container closure inspection to help guarantee the quality of their finished product.