# Container Closure Integrity Testing and Headspace Oxygen Monitoring in Pre-filled Syringes

LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

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## Introduction

This poster describes how laser-based headspace analysis is used for the rapid non-destructive determination of headspace oxygen levels in pre-filled syringes. Data is presented demonstrating two major applications of this technique: 1) headspace oxygen monitoring on a pre-filled syringe line filling oxygen-sensitive product, and 2) container closure integrity testing of pre-filled syringes.

## Headspace Oxygen Monitoring on a Pre-filled Syringe Filling Line

For a formulation that is oxygen sensitive, the filling process must be optimized to ensure that headspace oxygen levels are below specification. Optimizing and validating the process can be time consuming when using traditional headspace oxygen analysis methods. These are slow, destructive, and require being set up in a laboratory instead of at-line in the filling area. Pre-filled syringes provide additional challenges because of the small headspace volumes and the difficulty in accurately extracting the headspace gas for analysis. The portability and ease-of-use of a laser-based Oxygen Analyzer allows for set up next to the filling line enabling immediate feedback on the oxygen levels in the container headspace. Filling and purging parameters can be quickly optimized and validation data collected to demonstrate that the process is working to specification. Figure 1 shows headspace oxygen data collected on a pre-filled syringe line that was being validated in a new state-of-the-art parenteral facility. The 1ml glass syringe was purged with nitrogen before and during filling as well as at stoppering. The stopper was inserted into the syringe to leave a headspace of approximately 5 mm. Rapid non-destructive headspace oxygen analysis using a laser-based headspace system enabled optimization and monitoring of the purging process.

## Container Closure Integrity Inspection of Pre-filled Syringes

The inspection of headspace oxygen in syringes having a purged nitrogen headspace can also be used to determine whether the container closure integrity of the syringe has been maintained. A pre-filled syringe that has suffered from a closure integrity failure will immediately begin to diffuse air into the headspace. Defective syringes with high levels of headspace oxygen can then be detected and removed in an inspection process. Figure 2 shows how quickly headspace oxygen levels rise in a leaking 1ml container that is initially purged with nitrogen. Laser drilling was used to create known defects of certified sizes in the glass tubing barrel. The study took advantage of the non-destructive nature of laser-based headspace analysis to monitor headspace oxygen levels over time in individual samples. Figures 3 & 4 show data from a headspace oxygen study involving purged 0.5ml syringes. First, the efficiency of the purging and stoppering process was investigated as a function of the empty headspace size. Pre-filled syringe product samples were filled and stoppered with different stopper positions leaving empty headspace heights of 3, 5, 10, and 20mm. Figure 3 shows how efficient the nitrogen purging process was during filling in lowering the headspace oxygen content. It is clear that larger headspaces can be purged more efficiently. Figure 4 shows how the headspace oxygen levels evolve over time. Although no leakers were detected having atmospheric levels of oxygen, the syringes show a slow increase of headspace oxygen over time. This indicates a slower oxygen permeation process that, nevertheless, could be critical for oxygen-sensitive product.

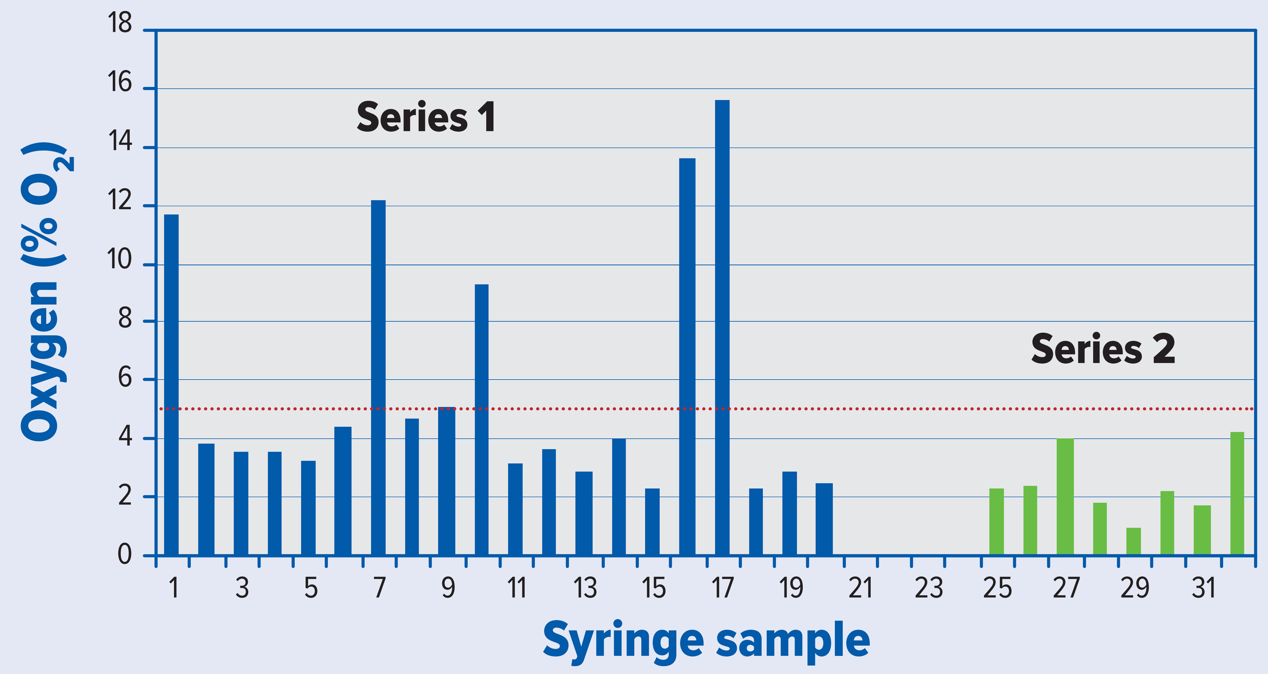


*Figure 1. Measured headspace oxygen in syringes filled on a line being validated in a new parenteral manufacturing facility. An initial series of syringes showed a number of syringes having headspace oxygen levels above the 5% specification. A later series showed the optimized process producing syringes with average headspace oxygen levels of 3%.*

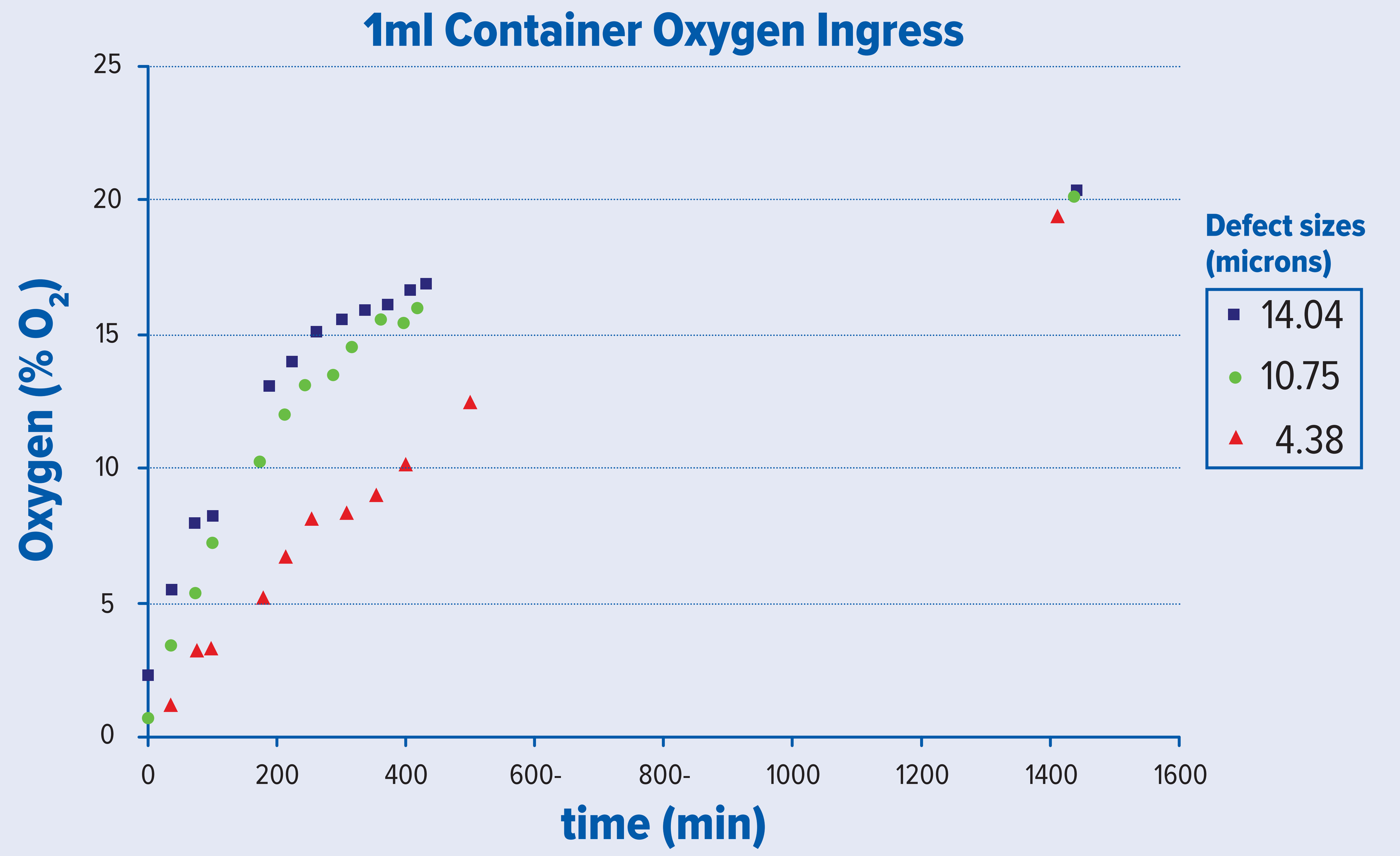


*Figure 2: The rise in oxygen levels in leaking 1ml containers that were initially purged with nitrogen as a function of time and defect size. After 24 hours, atmospheric levels of oxygen have been reached for all defect sizes. Elevated oxygen levels are clearly distinguishable from the initial low levels of oxygen demonstrating how a headspace oxygen measurement can be used to identify and reject leaking containers from the line.*

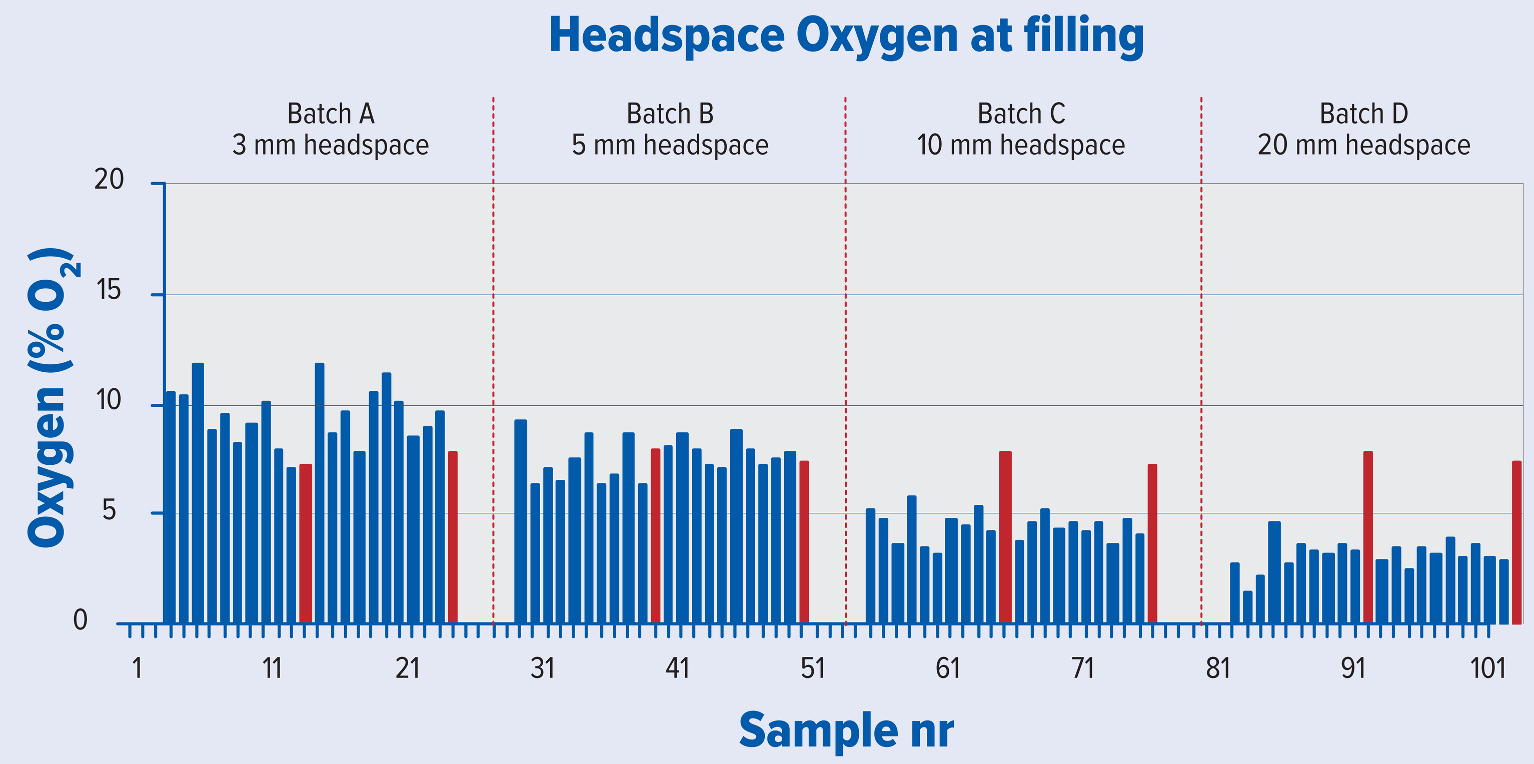


*Figure 3: Headspace oxygen measurments showing the purging efficiency during filling of the 0.5ml syringes as a function of the empty headspace height (stopper position). The values plotted in red are reference measurements made on a certified 8% oxygen standard.*

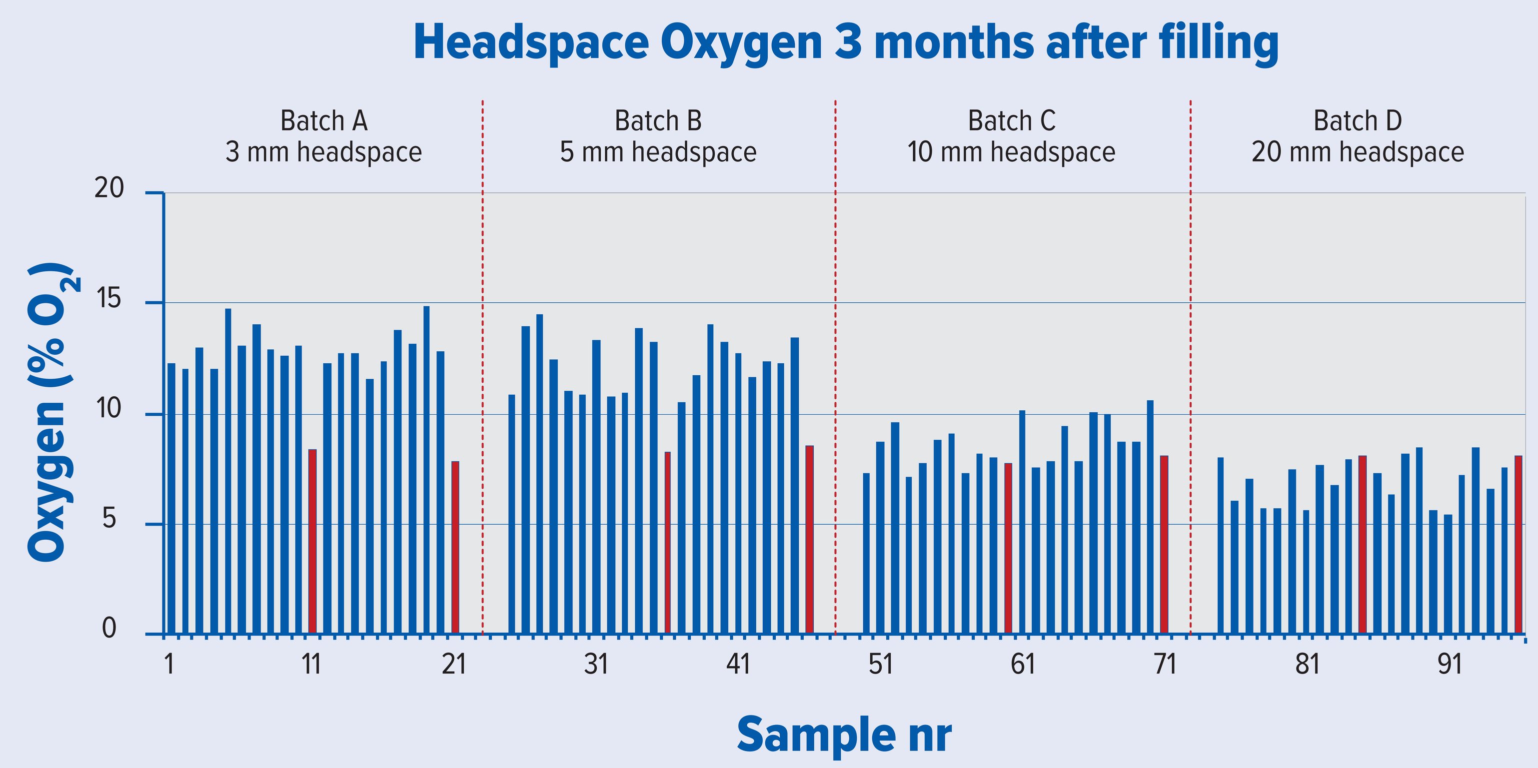


*Figure 4: Headspace oxygen measurements showing the slow increase of headspace oxygen levels over time in the 0.5ml syringes indicating a slow permeation of air into the syringe. The values plotted in red are reference measurements made on a certified 8% oxygen standard.*