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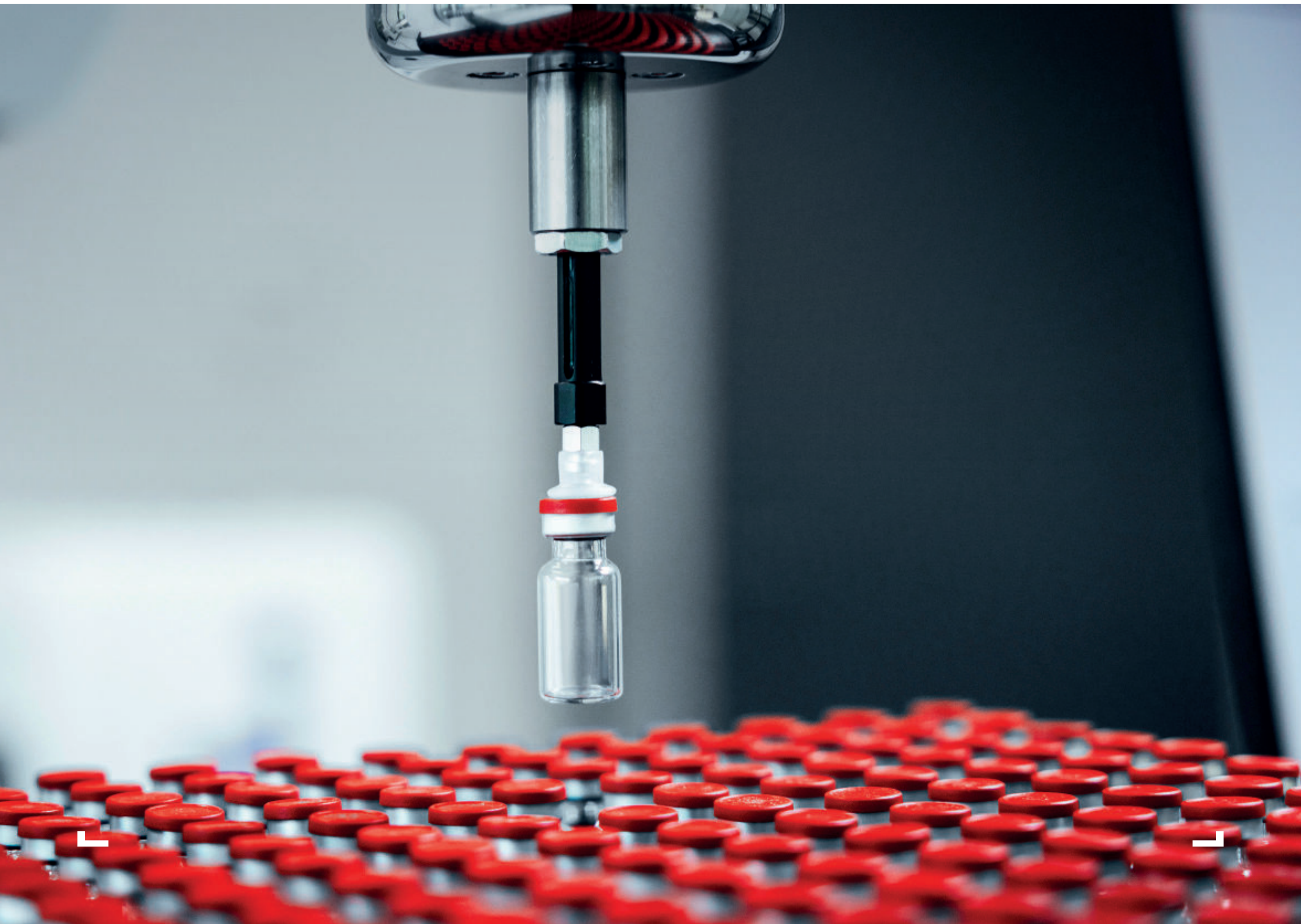
# Container Closure Integrity Testing

## Correlating Laser-Based Headspace Gas Ingress Testing to Helium Leak Rates



Driven by new regulatory requirements, industry best practices in the area of container closure integrity (CCI) testing are changing towards a science-based holistic approach, which includes the generation of robust container closure data throughout the product life cycle.

Therefore, a CCI test method capable of testing throughout the product life cycle is preferred over methods having a more limited application. A test method sometimes used to generate CCI data in early stages of package development is helium leak rate testing. While this method has the advantage of being very sensitive, it has its challenges when used in later stages of the product life cycle.

USP <1207>, Package Integrity Evaluation – Sterile Products, describes both laser-based headspace analysis (HSA) and helium leak rate (HeLR) testing as deterministic leak test technologies that can be used to test the CCI of sterile product-packages.

Both methods are capable of detecting an air leakage rate less than $1.4\times10^{-6}$ sccs, which corresponds to an idealized (circular) orifice with a flow-effective defect size of 0.1 µm, the lowest leakage rate provided in Table 1 of USP 1207.1. This article demonstrates a correlation between the two leak detection methods using proprietary positive control vials (designs based on Roche IP) with leak rates ranging from $10^{-6}$ to $10^{-8}$ sccs.

## EXPERIMENT

Both HeLR and HSA use tracer gas detection as a leak indicator. Instead of Helium, the HSA method described here uses carbon dioxide as the tracer gas.  A typical HeLR test set-up involves constantly purging a sample with helium at atmospheric pressure through an opening in the bottom of the container. The cap end is placed in a vacuum chamber which is sealed around the circumference of the vial body. The vacuum chamber is attached to a spectrometer, detecting a volume of helium over time (leak rate) above a specification in case of a CCI failure. A single sample is tested per run in this set-up. The positive controls tested for this experiment had leak rates of $10^{-8}$, $10^{-7}$, and $10^{-6}$ sccs, respectively.

The $CO_2$ headspace gas ingress method tested the same positive controls that were used during helium leak rate testing. For the $CO_2$ ingress test, samples were prepared having an initial headspace of 1 atm ambient air.

All samples were placed in a CCI test vessel which was then purged with carbon dioxide gas to displace ambient air inside the vessel and create a 100% carbon dioxide atmosphere in the test vessel. Once the purging process was complete, the vessel was pressurized to a total pressure of 2 atm carbon dioxide, and the samples were left in this environment during the remainder of the experiment unless measurements were being acquired. During each measurement session, the samples were removed from the CCI test vessel and their headspace carbon dioxide partial pressures were measured using an FMS-Carbon Dioxide Headspace Analyzer.

Once the measurements were complete, the samples were returned to the CCI test Vessel and the purging/overpressure procedure was repeated. By measuring the headspace carbon dioxide ingress over time, a carbon dioxide ingress rate (leak rate) was calculated (Victor et. al 2017).

## RESULTS

Figures 1 and 2 summarize the results for both the helium leak rate method and the carbon dioxide ingress method on a set of 2R and 10R glass vials having leak rates of $10^{-8}$, $10^{-7}$, and $10^{-6}$ sccs.

The $R^2$ coefficient was ≥0.98 for two separate repetitions of the experiment, demonstrating a strong correlation between the measured leak rates using the two CCI test methods.

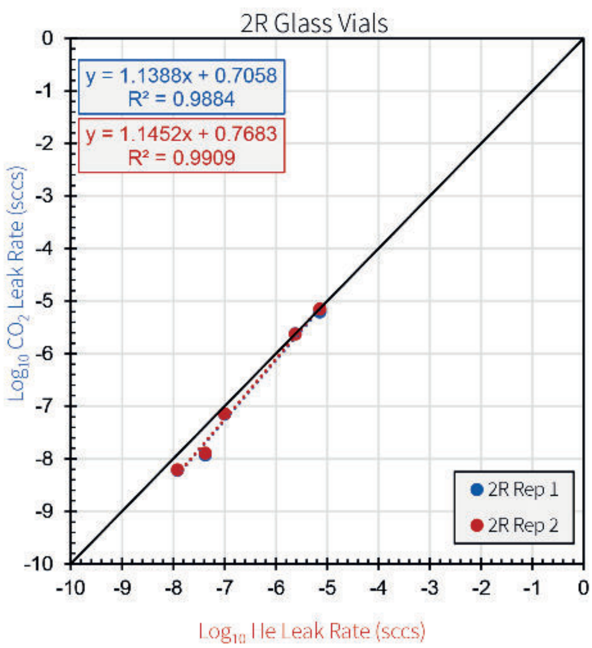



Figure 1: HeLR vs HSA for 2R glass vials.

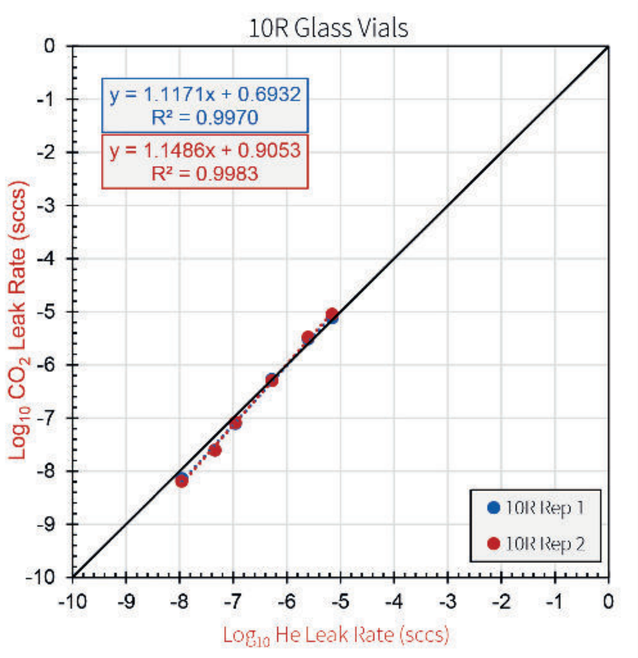



Figure 2: HeLR vs HSA for 10R glass vials.

## CONCLUSIONS

The described results demonstrate that laser-based headspace gas ingress testing is an equally sensitive leak detection method for CCI testing as HeLR. Using $CO_2$ as a tracer gas, leak rates as low as $10^{-8}$ sccs can be detected, which is two orders of magnitude less than the lowest leakage rate ($10^{-6}$) described in USP <1207>. While helium leak testing does have high sensitivity, only one sample at a time may be conditioned and tested, it is destructive, and sample preparation can become time-consuming.

Headspace gas ingress testing has the advantage over helium leak rate testing in that it is non-destructive, can be configured for higher throughput to generate data on statistically relevant sample sets, and actual product samples can be tested. It can be used throughout the complete product life cycle, with the capability of generating robust science-based container closure data on (product-filled) samples.

## REFERENCES

[1] K. Victor, M. Timmins and J. Veale, "Method Development for Container Closure Integrity Evaluation via Headspace Gas Ingress by Using Frequency Modulation Spectroscopy," PDA J. Pharm. Sci. Technol., vol. 71, no. 6, p. 429, 2017.

[2] C. Proff, H. Röhl, A. Caudill, J. Nunkaew, K. Victor, "Correlating CCI Leak Rates as Determined by Helium Leak Testing and Laser-Based Headspace Carbon Dioxide Analysis Using Modular Positive Controls", 2023 PDA Parenteral Packaging Conference, 18-19 April 2023.

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