

## CASE STUDY

Ensuring Container Closure Integrity (CCI) for Products requiring Deep Cold Storage by correlating Seal Quality to CCI





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# Background

The increased implementation of deterministic analytical methods for container closure integrity (CCI) testing has enabled deeper insight into the performance of primary packaging with respect to CCI. However, ensuring good CCI of sterile injectable product goes beyond CCI testing during the product life cycle.

As described in USP <1207.3> Package Seal Quality Test Methods, the measurement of residual seal force (RSF) indicates the quality of the vial package seal, giving insight into the quality of the sealing process. Correlating RSF to CCI data enables optimization and validation of the vial sealing process with parameters that give assurance of good CCI.

This Case Study describes how packaging development and process study data of a pharmaceutical vial product requiring deep cold storage can be combined in a holistic approach. Science-based statistically valid RSF data was generated on the vial sealing process and combined with CCI data throughout the product life cycle to ensure good CCI.



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# Experiment

Carefully designed CCI studies were performed on statistically valid sample sets consisting of stoppered vials prepared with different capping & crimping settings. Four different settings were used to cover a range of loosely to tightly capped and crimped vials.

Different vial-stopper combinations were used to investigate if there were specific primary packaging components that delivered optimum CCI performance at the deep cold storage temperature.

A headspace CCI test method was developed to test samples in deep cold storage (-80°C). The samples were placed in a -80°C freezer containing dry ice. The dry ice created a carbon dioxide (CO<sub>2</sub>) rich atmosphere in the storage environment, which means that any leaking containers would ingress CO<sub>2</sub> during storage. An increase of CO<sub>2</sub> measured in a vial sample after storage indicated a leaking container.

If no significant increase in CO<sub>2</sub> levels was measured after the storage period, the packaging was considered to have remained intact. In this scenario, CO<sub>2</sub> served as a tracer gas for leaks and headspace CO<sub>2</sub> measurements performed directly after deep cold storage served as a CCI indicator.

Figure 1 shows how this headspace CCI method detected various types of positive control leak defects by measuring the amount of CO<sub>2</sub> that had ingressed into the vial through a leak. The control samples in this CCI data set included microwires placed between the stopper and vial neck creating an undefined (sub) micron leak, laser-drilled vials having well-defined micron hole leaks in the vial body, gross leak samples, and negative controls (1).

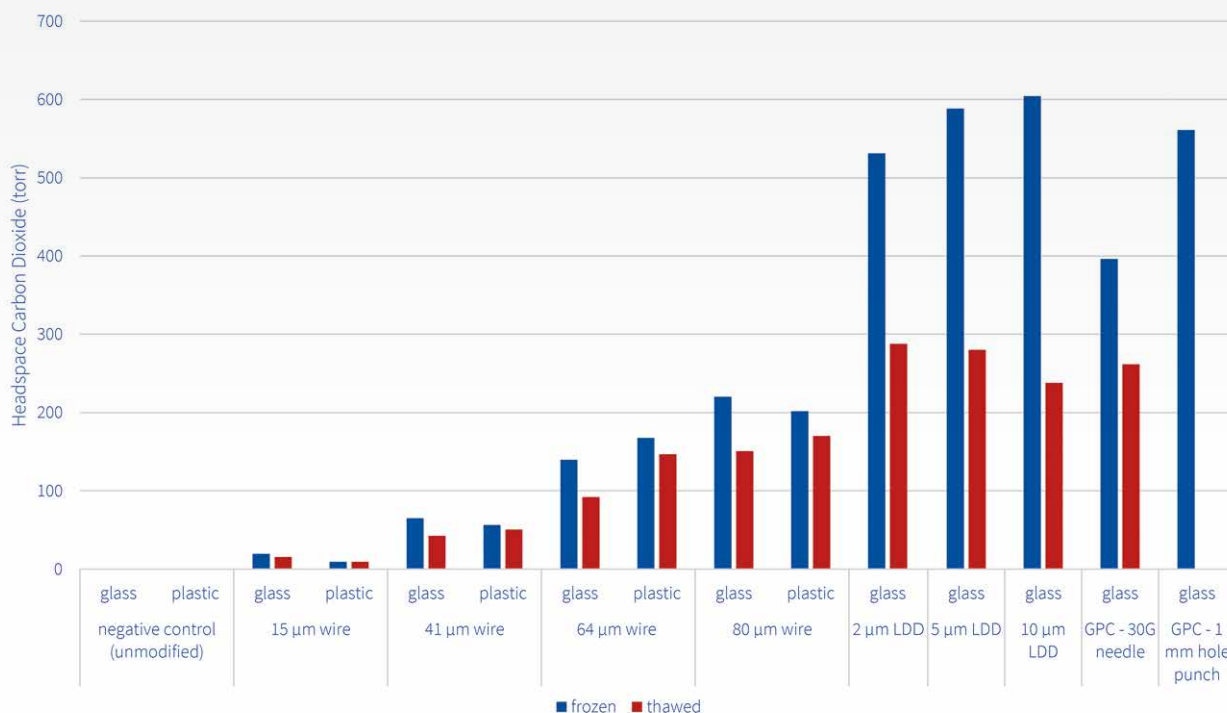


Figure 1. Plot of measurements demonstrating how a headspace CCI test method identifies various positive controls as leaking vials by detecting CO<sub>2</sub> gas ingress.



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In addition to CCI testing, RSF testing was performed as a seal quality test to measure the force that is exerted by the stopper on the vial flange surface after the vial is capped and crimped. Since CCI of vials depends on the quality of the seal, various capping & crimping settings were used to produce samples over a wide range of RSF values corresponding to vials that were loosely to tightly sealed. After storage at  $-80^{\circ}\text{C}$ , the samples were tested for maintenance of CCI using the developed non-destructive headspace  $\text{CO}_2$  method.

Figure 2 shows measured RSF values as a function of four different crimping pressures/settings used to seal the vials for vial-stopper combination X. Samples failing the headspace CCI test after deep cold storage are plotted in red – the blue data points are samples that passed the CCI test. This statistical RSF-headspace CCI correlation data shows high CCI failure rates of these primary packaging components if the components are not tightly capped and crimped (1).

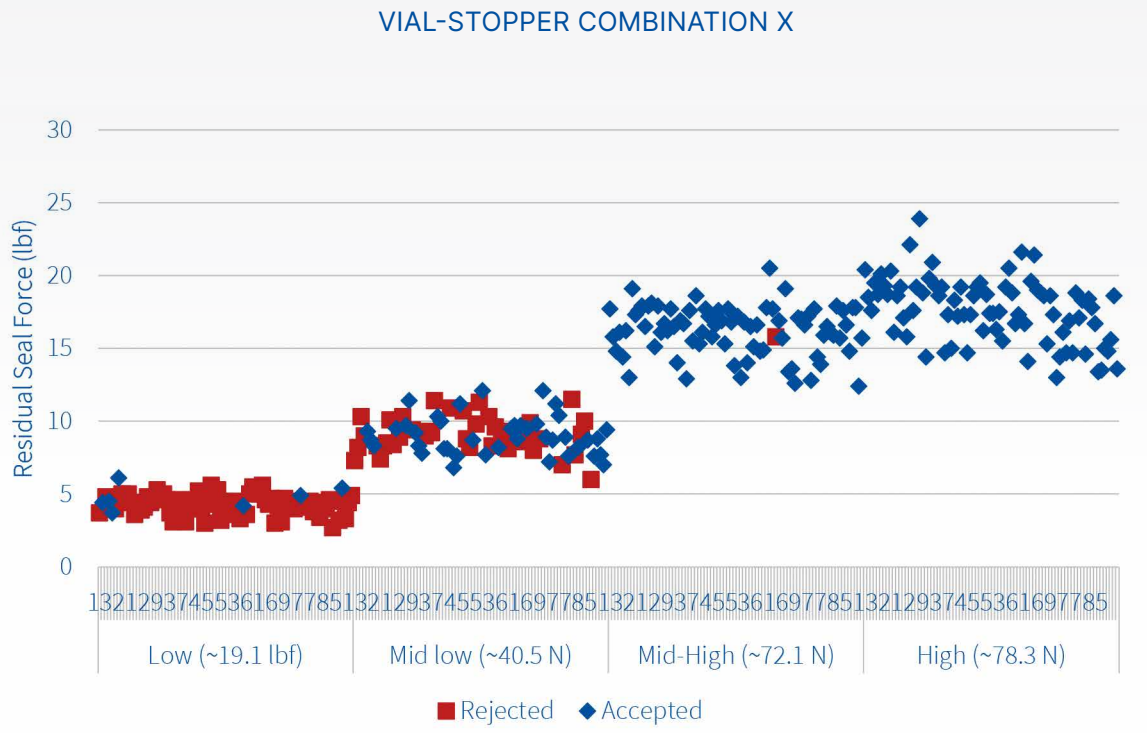


Figure 2: RSF-CCI correlation data of vial-stopper combination X. The red data points indicate samples that lost CCI during deep cold storage.



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Figure 3 again shows measured RSF values as a function of four different crimping pressures/settings used to seal the vials but now for vial-stopper combination Y. Samples that passed the headspace CCI test after deep cold storage are plotted in blue. Contrary to the results of sample set X, the statistical RSF-headspace CCI correlation data for sample set Y reveals a retention of CCI during deep cold storage over the full range of capping & crimping settings and corresponding RSF values – even when loosely capped & crimped (1).

Robust packaging and process development studies, such as those described here, where statistically valid correlations between seal quality and CCI are generated, enable manufacturers to make science-based decisions about the primary packaging components and the vial sealing process.

From the data plotted in Figure 2, it is immediately clear that vial-stopper combination X requires consistently high RSF values (tightly capped & crimped) to maintain good CCI during deep cold storage. On the other hand, the results for vial-stopper combination Y plotted in Figure 3 demonstrate that these primary packaging components maintained good CCI over the full range of RSF values meaning that, for this vial-stopper combination, the vial sealing process can be validated with a much larger process design space that delivers good CCI.

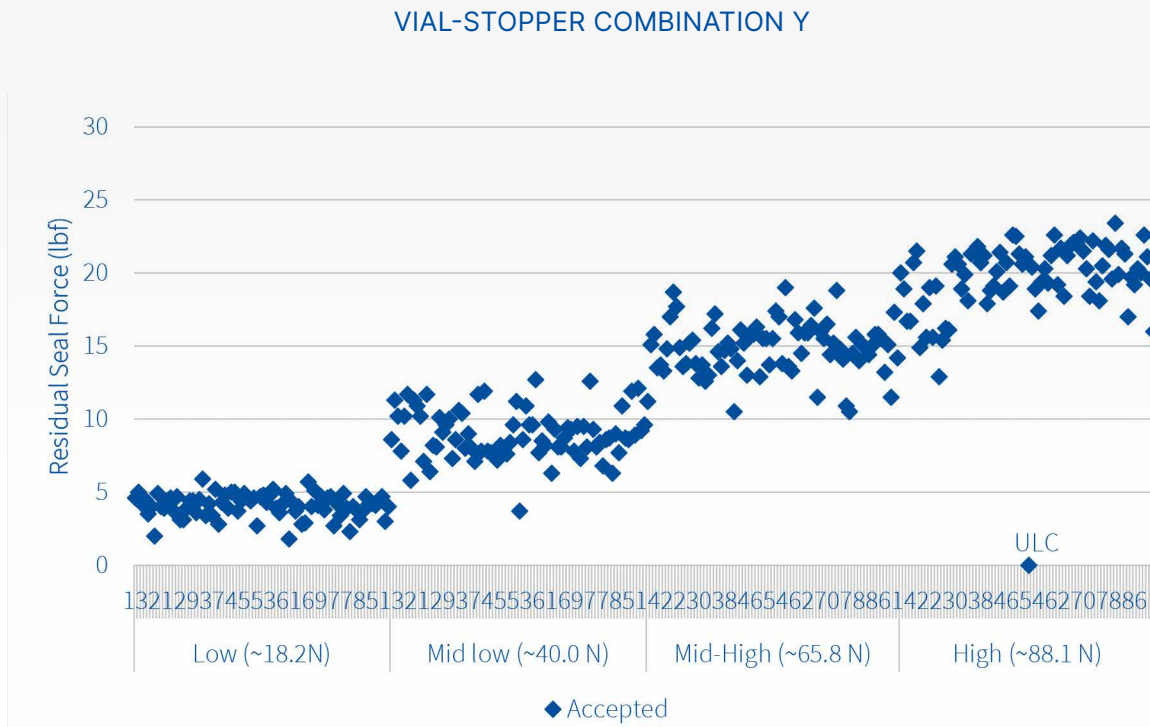


Figure 3: RSF-CCI correlation data of vial-stopper combination Y. All samples maintained CCI during deep cold storage.



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# Conclusions

- Combining Residual Seal Force (RSF) measurements with container closure integrity (CCI) testing provides valuable/deep insight into the suitability of primary packaging components and capping & crimping parameters.
- By generating statistically relevant data sets, manufacturers of sterile vial products are able to design robust manufacturing processes that ensure CCI of their products – even for deep cold storage conditions.
- The ability to generate robust data, using RSF for sealing quality and non-destructive headspace analysis for CCI, can assist in various product life cycle activities including: the choice of appropriate primary packaging components, validation of the capping & crimping process, and implementation of an effective CCI control strategy.





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## REFERENCES

- [1] D. Duncan and R. Asselta, Parenteral Drug Association Webinar “Container Closure Integrity of Product Requiring Deep Cold Storage at -80°C”, October 1, 2020.

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