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CASE STUDY

Container Closure Integrity (CCI) Test Method Development for Autoinjectors with an Optically Transparent Window

Introduction

- Ionis Pharmaceuticals packages its drug product in an autoinjector with a 1mL long glass prefilled syringe. They recognized the need for a robust CCI test method and turned to Lighthouse for invaluable assistance.
- The pharmaceutical industry increasingly relies on prefilled syringes and autoinjector configurations as the product mix shifts to biological medications. Combined with demand from clinicians to increase ease of use and decrease dosing errors, there has been a significant increase in the popularity of PFS and autoinjector product configurations.
- Laser-based headspace analysis is a powerful tool for CCI testing on PFS and autoinjector configurations.

STUDY OBJECTIVE

Existing methods for testing CCI in autoinjectors have several issues: they typically require disassembly, are destructive, and can be difficult to validate. Because of the difficulties in directly assessing the CCI of a fully assembled autoinjector, many manufacturers remove the PFS from the autoinjector assembly so that they can conduct the CCI test on just the pre-filled syringe itself. This case study aims to demonstrate how a Lighthouse non-destructive CCIT method using headspace carbon dioxide measurements can be used on autoinjectors with an optically transparent window.

The project aimed to develop a USP <1207> compliant method to evaluate CCI for an Ionis autoinjector configuration during storage at 5 ±3°C. Note that this method can be readily altered to evaluate the CCI of this configuration when stored at ambient conditions.

The CCIT method has two steps:

1 To condition the samples in a pressurized vessel to effusively drive the carbon dioxide gas tracer through any leaks in the sealed pre-filled syringe.

2 To measure the samples for headspace carbon dioxide. An increase in the headspace carbon dioxide content of a sample or control is used to identify a breach in its CCI.

TABLE 1: Sample matrix for the Ionis sample set.

Sample		**Sample Preparation**		**Defect**		**Conditioning Environment**
GROUP	TYPE	FILL	HEADSPACE	TYPE	SIZE	
1	Micron Positive Control	Empty	Ambient Air	Laser-Drilled	5 µm	5°C 8 psig CO_2 60 minutes
2	Type Control	0.8 mL Water			10 µm	
3	Type Control	0.8 mL Water			15 µm	
4	Gross Positive Control	Empty		22G × ⅜" Syringe Needle‡	413 µm	
5	Gross Positive Control	0.8 mL Water				
6	Unmodified Control	Empty		None	N/A	
7	Test Sample	0.8 mL Water				
8	Negative Control	Empty				Ambient Air
9	Negative Control	0.8 mL Water				

‡ 22G × ⅜ inch syringe needle (Air-Tite Ref# N2238). The syringe needles were cut to remove the luer lock to fit within the autoinjector assembly.

CCI TEST METHOD DEVELOPMENT

Ionis prepared the 70 controls and test samples used in the study. The sample set consisted of nine different Sample Groups, as detailed in Table 1.

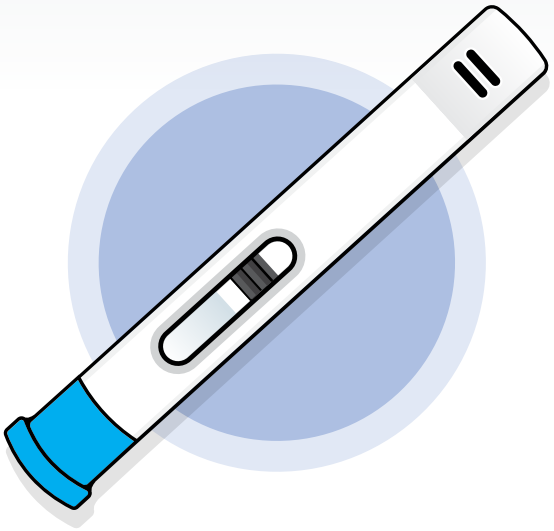
The six main parameters associated with sample conditioning inside the vessel are the initial purge rate of the carbon dioxide tracer gas, the length of the purge, the length of time allowing the initial purge to mix in the chamber, the gas's overpressure, the time period the samples are exposed to the overpressure, and the number of samples placed inside the chamber for conditioning. Lighthouse determined the appropriate values for each.

The accept/reject limit was determined based on the minimum amount of carbon dioxide required to confidently identify a change in the headspace carbon dioxide content of a sample and, thereby, the presence of a breach in the autoinjector assembly CCI.

Only empty versions of the laser-drilled positive controls with a 5 µm flow-effective size were considered positive controls for a number of reasons.

First, from a quality risk assessment analysis, the probability that a loss of CCI is caused by a single micron-sized "pinhole" defect in the wall of the container is relatively small when compared to the probability that the breach in CCI is caused by a failure at the plunger-seal interface. Defects in the glass or plastic wall of a container are typically relatively large, visible cracks created during the production and packaging process. In other words, because laser-drilled defects do not represent typical "real-world" defects, the ability to detect such defects below the liquid fill does not provide results/information that is directly relevant to evaluating the CCIT Method.

Second, because their flow-effective size can be certified ("Certificate of Calibration") by an independent party (Lenox Laser), the use of laser-drilled defects is a pharmaceutical industry standard when evaluating a CCIT method. However, because of the inherent physical instability of such defects, the Certificate of Calibration for each laser-drilled defect includes the



caution statement "Do not expose the calibrated orifice to moisture, vapors, or particulates." In other words, this suggests that the introduction of a liquid product to the container containing the laser-drilled defect essentially invalidates its Certificate of Calibration because of the potential for the liquid to physically alter the defect itself.

Third, because the empty positive controls have the maximum headspace volume, they represent the "worst-case" scenario with respect to observing a change in the headspace content for a given defect size.

The final rationale is recognizing that the potential of the product to inhibit the identification of a defect is an inherently probabilistic event that depends upon the product itself, the defect geometry and location, and the sample handling and storage history. Because quantifying these probabilistic events across the full spectrum of defect geometries and locations is problematic at best and beyond the scope of this CCIT method development, it must always be acknowledged that the possibility exists that a given product may prevent the identification of a particular defect, regardless of the CCIT method that is employed.

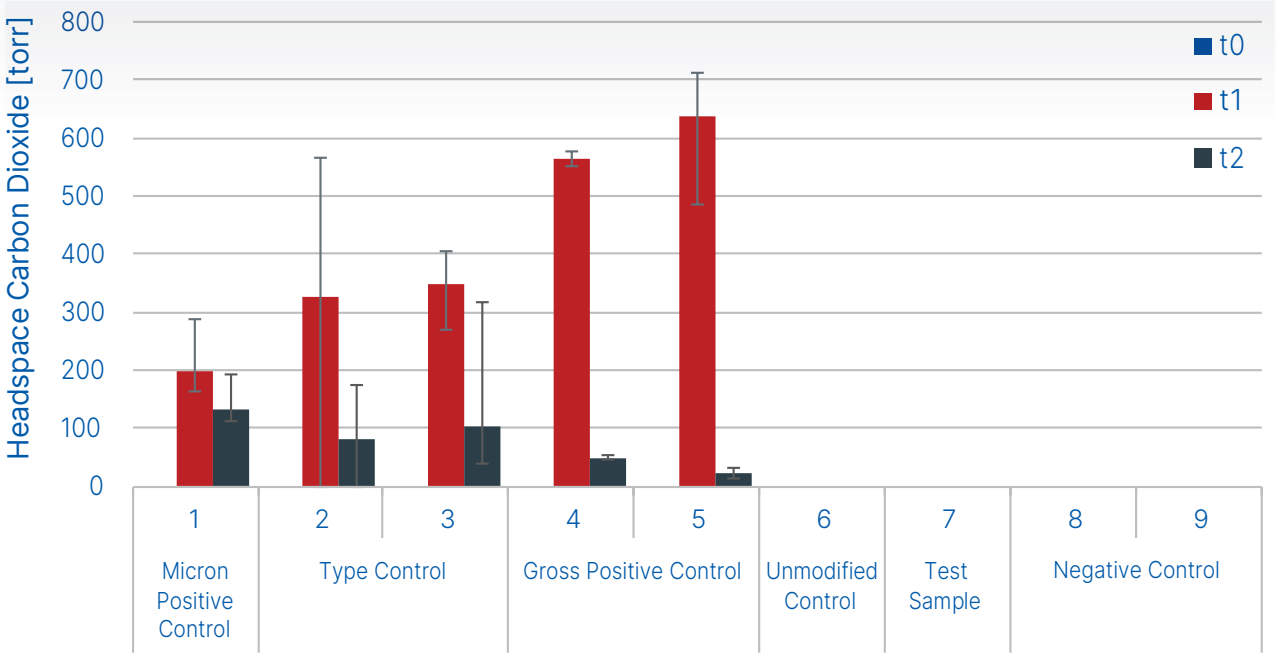


FIGURE 1: Shown are the results of the nondestructive headspace carbon dioxide analysis by control group. Significant amounts of CO_2 were detected in the samples of the positive control groups immediately after removing them (T1) from the pressurized conditioning vessel which identified them as leaking samples. After a couple of hours in ambient air conditions (T2), measurable amounts of CO_2 were still present in the leaking samples. In contrast, the negative and unmodified control groups showed no ingress of CO_2.

Additional laser-drilled controls were prepared with both a 10 and 15 µm flow-effective size that were exposed to liquid product formulation. These serve as "type controls" to demonstrate that a submerged defect can be found. "Type Defects" are described in USP <1207.1> Section 4.5.2 as representing package flaws that, because of their inherent irregularity and complexity (e.g., the change in the flow-effective size of a laser-drilled defect due to exposure to a liquid), cannot be assigned well-characterized sizes and, thus, cannot be treated as certified positive controls.

The samples were nondestructively measured for headspace carbon dioxide levels using a Lighthouse Instruments FMS-Carbon Dioxide Headspace Analyzer to establish a baseline carbon dioxide content. Each sample was measured 5 consecutive times each. The samples were then placed into a Lighthouse 8L CCI Test (pressure) Vessel and overpressured to 8 ±1 psig. The entire 8L CCI Test Vessel was placed in a 5 ±3°C refrigerator and held for a period of 60 minutes. All controls (except the negative controls) and test samples were conditioned in the vessel for the 60-minutes period.

After executing this 60-minute conditioning protocol, the overpressure was released, and the samples were removed. The headspace carbon dioxide content of all controls and samples was remeasured immediately upon removal from the vessel. The results, both before and after sample conditioning, are summarized in Figure 1.

CASE STUDY CONCLUSIONS

The results from this experiment indicate that this nondestructive CCIT Method can robustly identify leak defects with a flow-effective size down to 5 µm in the Ionis autoinjector configuration. All positive controls were readily identified as having a breach in CCI because all exhibited a significant change in their headspace carbon dioxide content. Conversely, all unmodified and negative controls were identified as having maintained CCI because none exhibited a change in their headspace carbon dioxide content. Finally, 4 of the 5 type defects with the submerged 10 µm laser-drilled defects showed a measurable increase in headspace carbon dioxide.

In summary, this case study demonstrated that a nondestructive CCIT Method using headspace carbon dioxide analysis can be used to directly evaluate the CCI of a fully assembled autoinjector configuration with a pre-filled syringe when it has an optically transparent window. As always, the CCIT Method parameters can be adjusted depending on the specifics of a configuration, as appropriate to meet the quality requirements. This CCIT Method is appropriate for all phases of the product life cycle, from initial inherent CCI, through manufacturing and release, and into stability.

REFERENCES

[1] Victor, K., Levac, L., Timmins, M., and Veale, J. *"Method Development for Container Closure Integrity Evaluation via Headspace Gas Ingress by Using Frequency Modulation Spectroscopy"* PDA J. Pharm. Sci. Technol. 2017, 71 (6), 429-453.

[2] Caudill, A., Victor, K., Timmins, M., and Veale, J. *"Container Closure Integrity Test using Frequency Modulation Spectroscopy Headspace Analysis with Carbon Dioxide as a Tracer Gas"* PDA J. Pharm. Sci. Technol. 2021, 75 (2), 157-172.

CONTACT US

- Lighthouse Instruments, LLC
  2050 Avon Court
  Charlottesville, VA 22902
  United States of America
  Office • +1 (434) 293-3081
  Email • info@lighthouseinstruments.com

  www.lighthouseinstruments.com

- Lighthouse Instruments B.V.
  Wisselwerking 22
  1112 XP, Diemen
  The Netherlands
  Office • +31 (0)20 7051 050
  Email • euinfo@lighthouseinstruments.com