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CCI testing throughout the product life-cycle

Using laser-based headspace analysis

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The tale of the freeze-dried product that lost vacuum

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The product & the problem

Product specifications

Freeze dried, closed at 0.2 atm nitrogen

Problem

QC identified vials that had lost vacuum.

- Packaging problem?
- Process problem?

Decision

100% CCI inspection of 6 batches

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100% CCI inspection of 6 batches

Requirements

- Save as much product as possible
  - Non-destructive measurement
- Time = money, so measure fast!
  - Rapid measurement

} Laser-based headspace analysis

Demonstrate loss in CCI?

- Increase in pressure
- Increase in oxygen

} Laser-based headspace analysis

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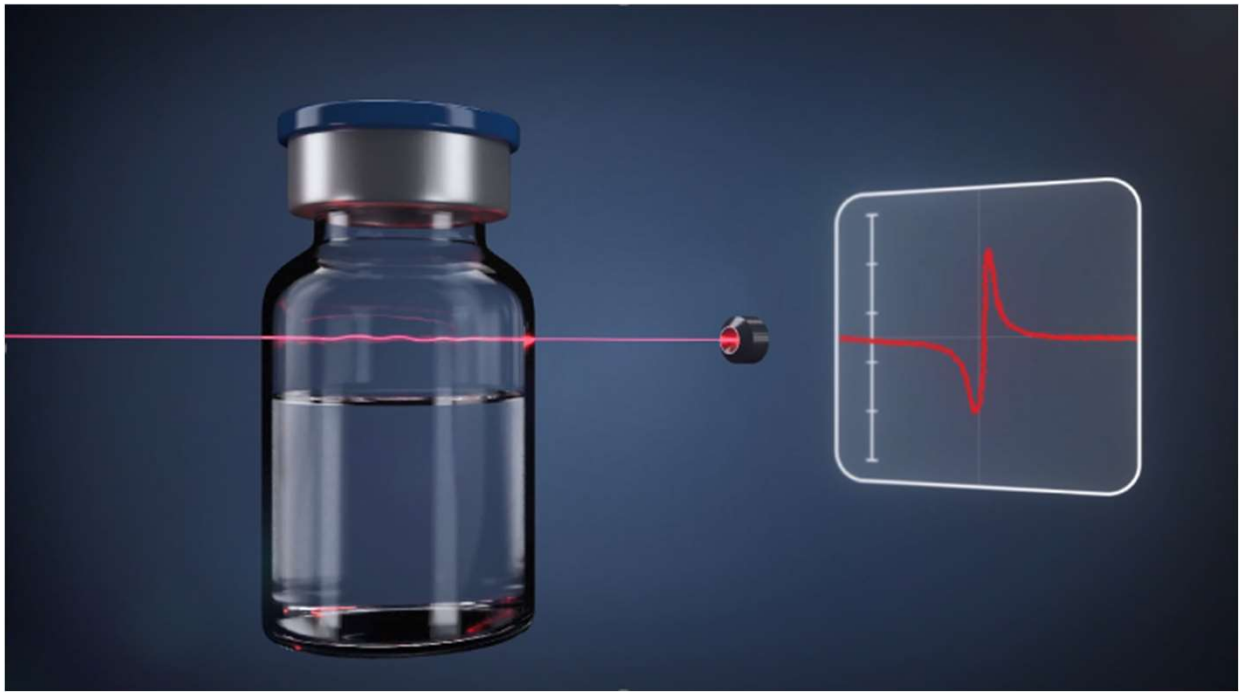
Laser-based headspace analysis



- Oxygen
- Pressure
- Carbon dioxide

- Non-destructively, in seconds

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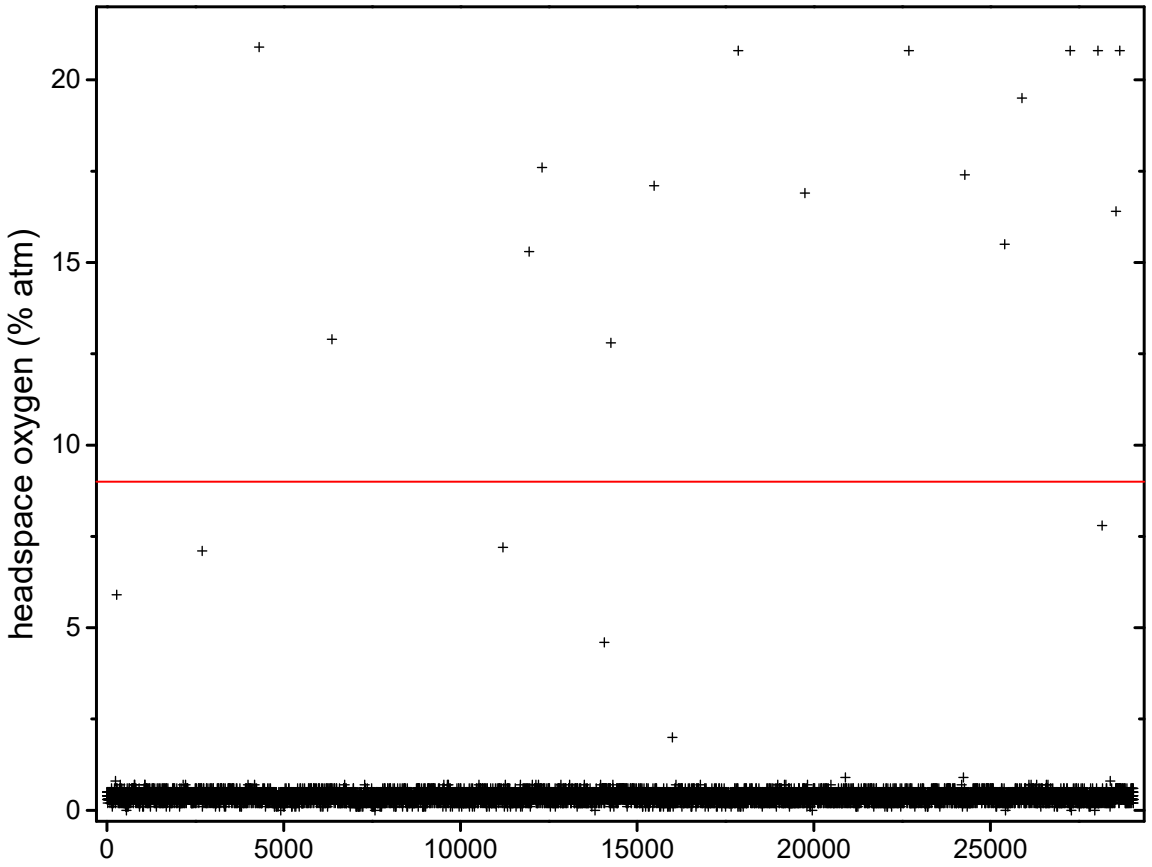
What sort of packaging?

- Anything that **lets through laser light**
- Can be plastic or glass
- Containing solid or liquid product

- Has a **headspace**…

100% CCI testing: Measure oxygen



Total batch size: 29048
Reject: 0.06%

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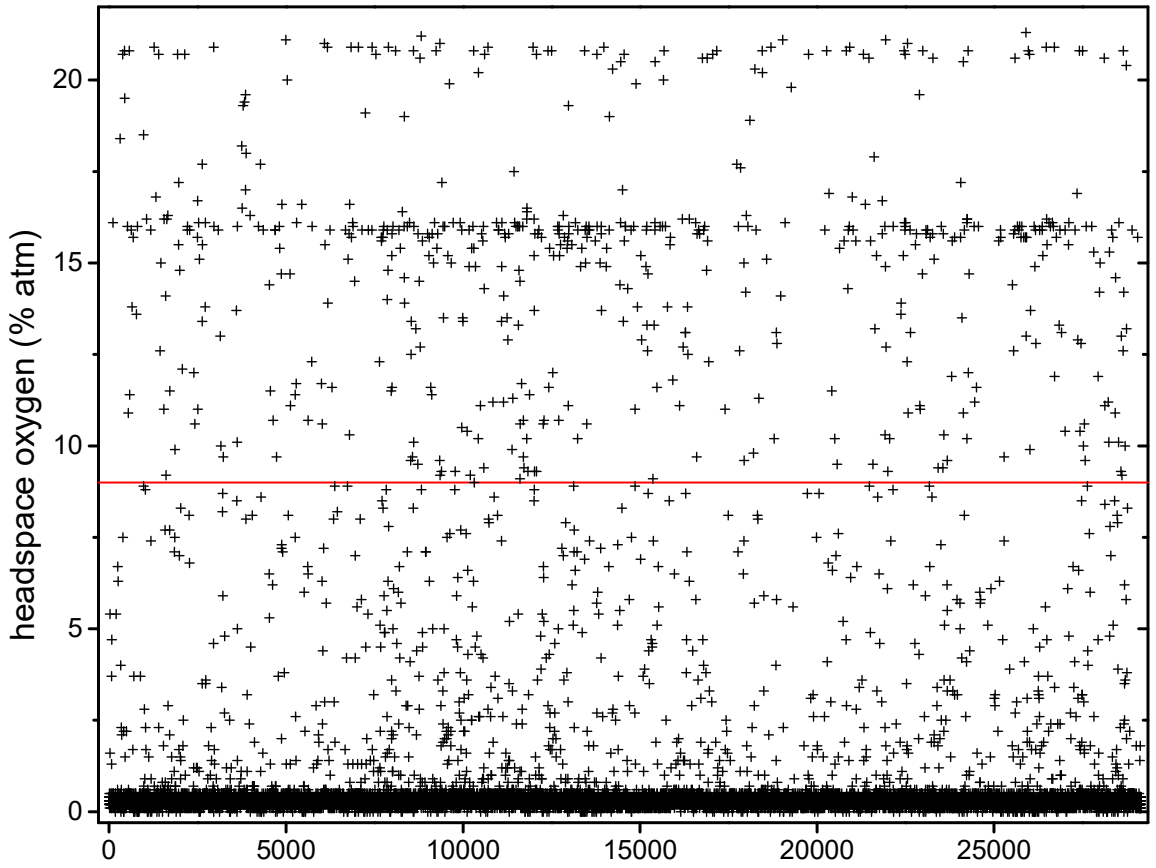
100% CCI testing: Measure oxygen

- Same vial…
- Same stopper…
- Same process…



Total batch size: 29156
Reject: 1.95%

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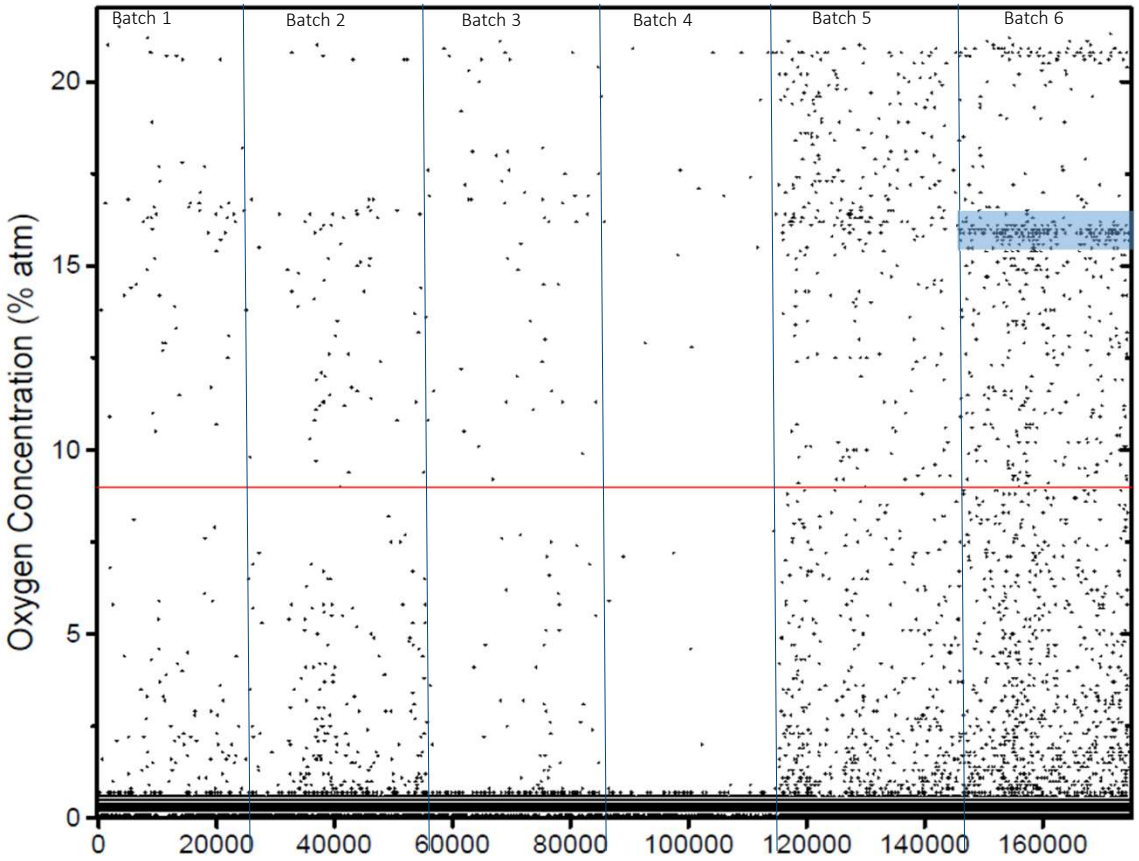
100% CCI testing: Measure oxygen



Not a robust process!

When would you prefer to discover this?

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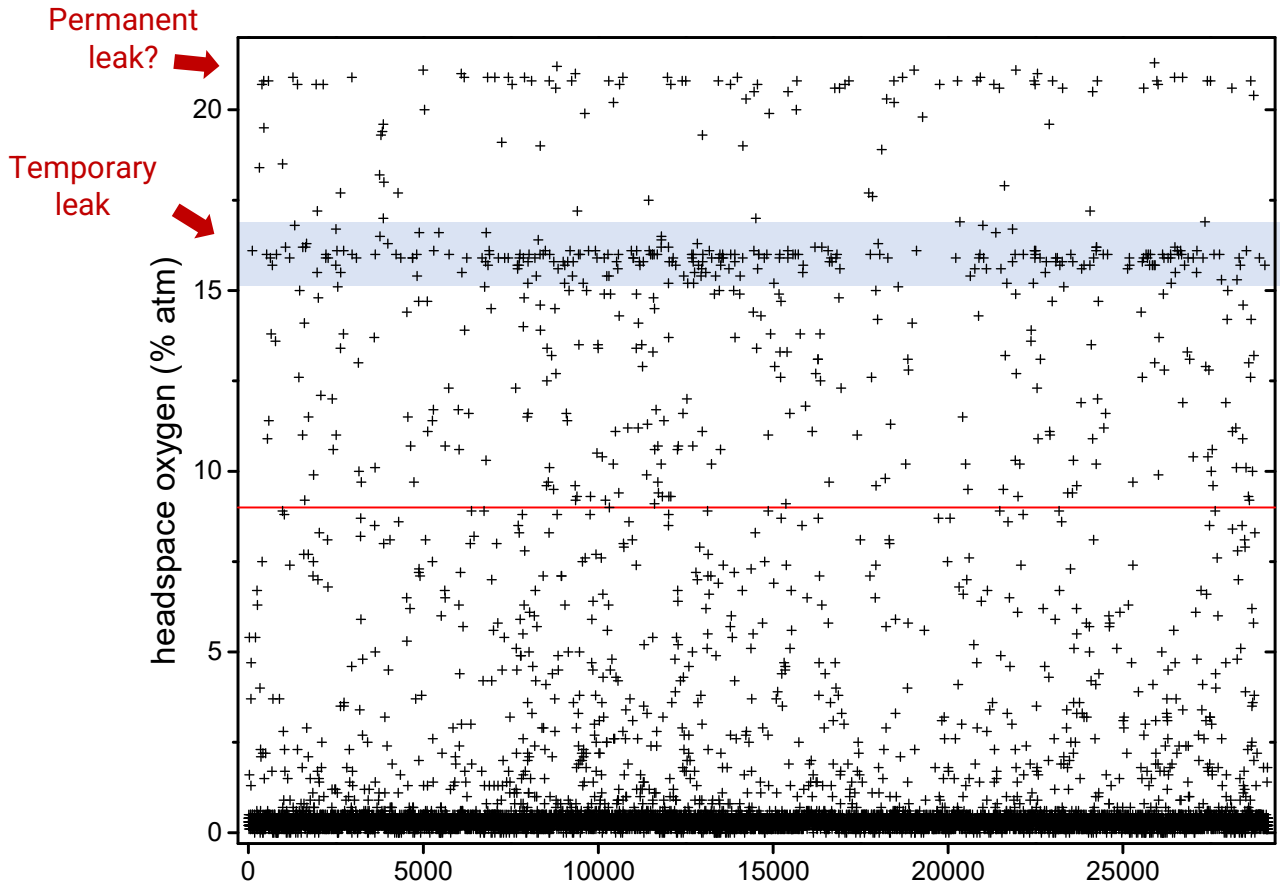
Temporary leaks



Why 16%?

Start: 0.2 atm N_2

Leak: 0.8 atm **air**

0.64 atm N_2 + 0.16 atm O_2

1.0 atm

+

Temporary leaks are difficult to detect when the applied seal is intact

Gas flow dynamics

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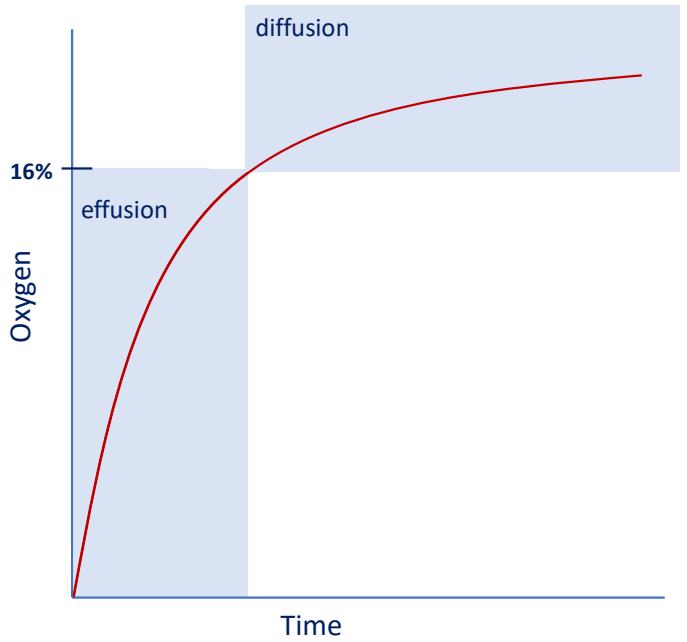
Two ways gas can flow

Effusion

Gas flow driven by a total pressure difference across the defect = ***FAST***

Diffusion

Gas flow driven by a partial pressure difference of that gas across the defect = ***SLOW***



PDA Journal of Pharmaceutical Science and Technology

Method Development for Container Closure Integrity Evaluation via Headspace Gas Ingress by Using Frequency Modulation Spectroscopy

Ken G. Victor, Lauren Levac, Michael Timmins, et al.

PDA J Pharm Sci and Tech **2017**, *71* 429-453
Access the most recent version at doi:10.5731/pdajpst.2017.007518

Understand gas flow to develop CCI test methods based on gas ingress

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The tale of the vaccine that escaped its package

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The call you don't want to get…

Another type of temporary leak

- At -80 °C the headspace shrinks and creates an **underpressure**
- The stopper loses its elastic properties and closure can be lost
- Cold dense CO_2 from environment fills headspace
- Warming to room temperature **reseals** the vial
- Trapped & expanding CO_2 creates an **overpressure**

There has been a leak, but the seal is intact.
Dye ingress cannot detect this!

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Why does this happen?

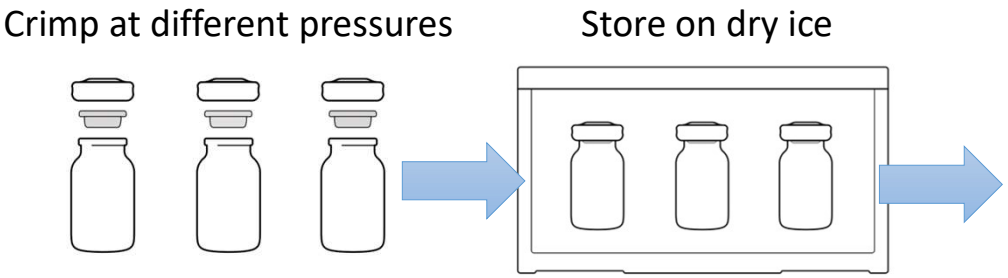
Packaging failure

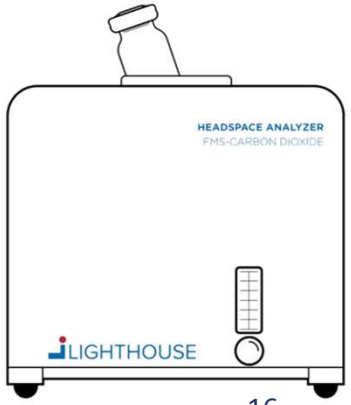
- Aluminum cap material
- Stopper material
- Stopper-vial dimensional fit

Process failure

- Inconsistent crimping
  - Seal quality testing + CCI testing

How?





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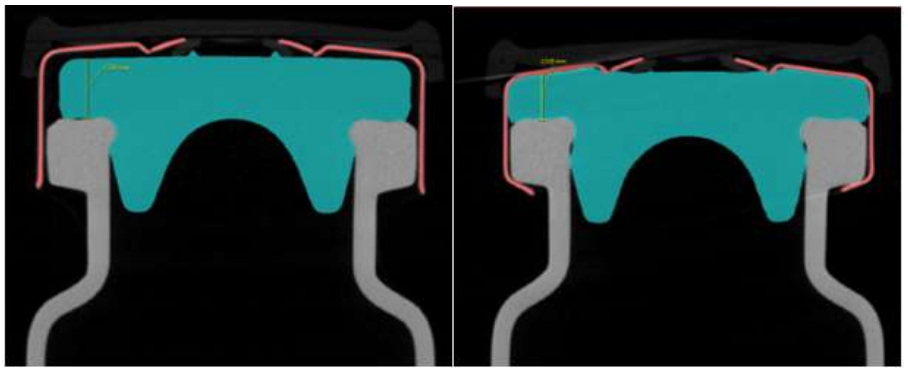
Residual Seal Force

- In sealing rubber components, the **elastic property** is important.
- An applied stress (sealing force) induces a corresponding strain which creates a contact stress.
- This **stored internal energy** is the Residual Seal Force (RSF).



Source: Genesis Packaging Technologies

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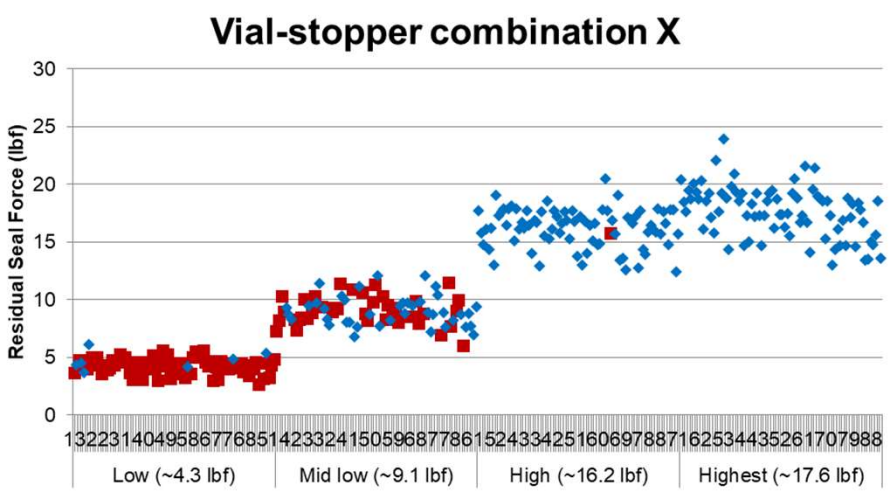
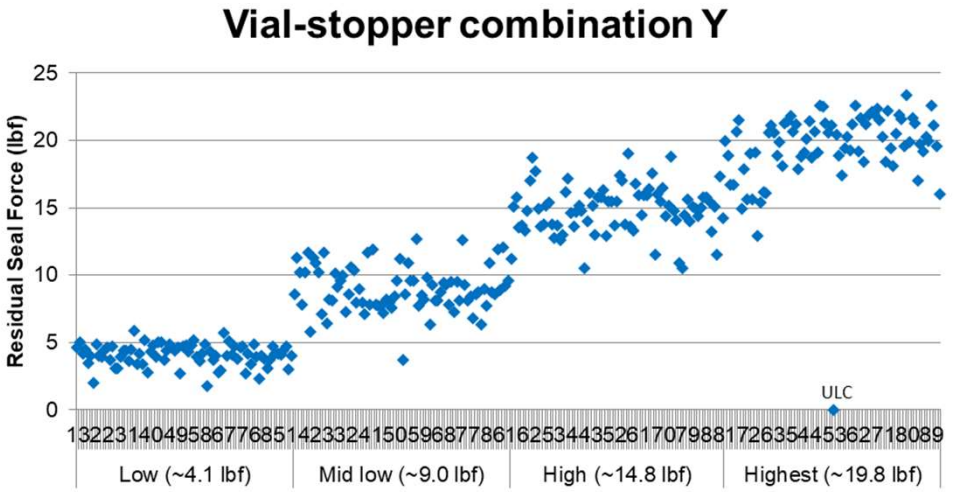
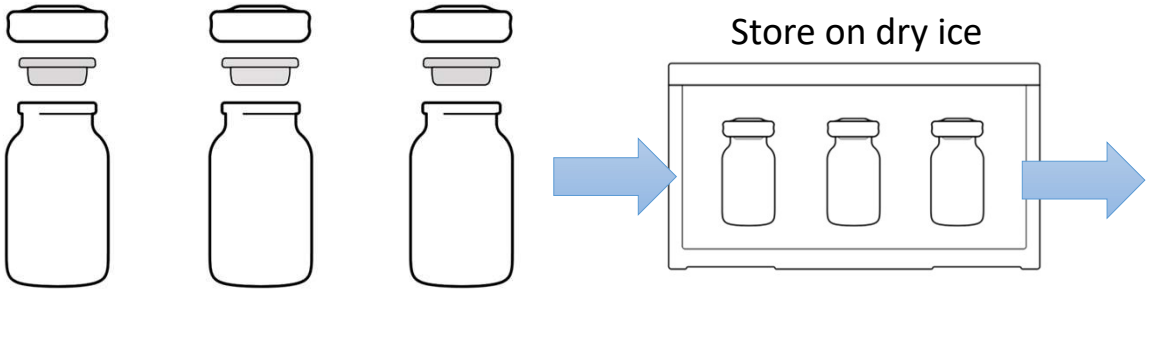
Correlating seal quality to CCI







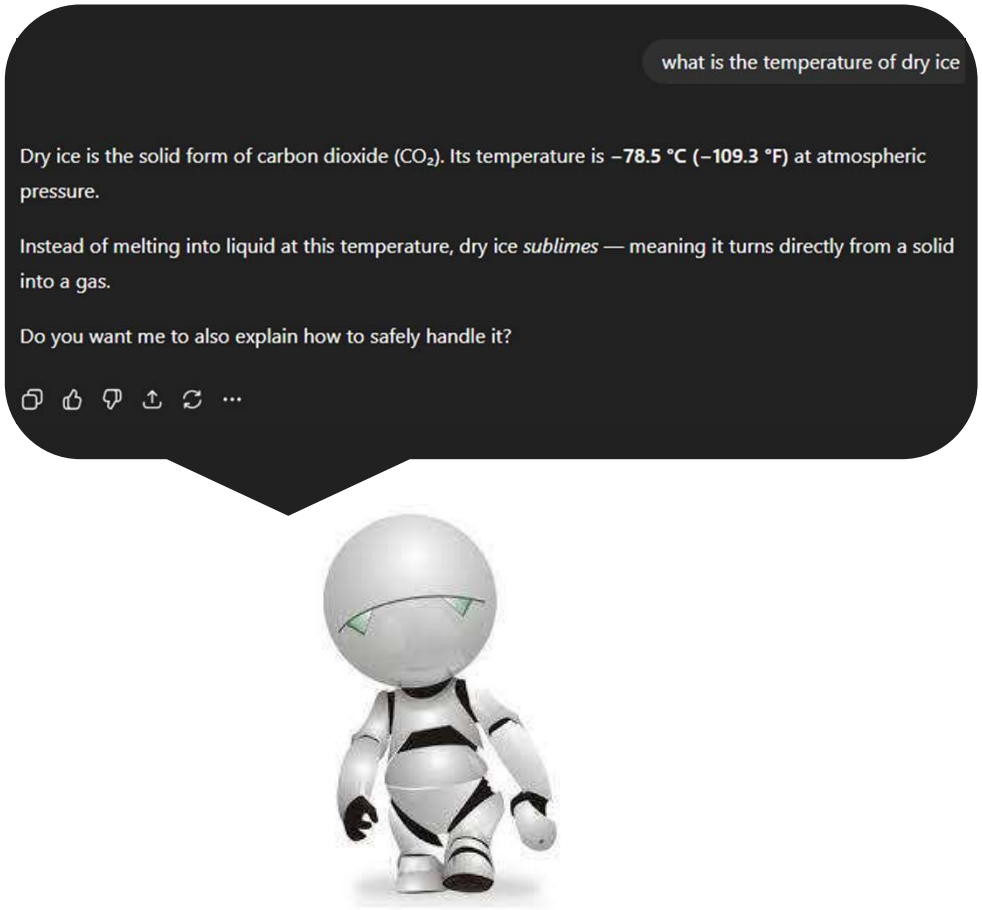
Quiz…

What is the temperature of dry ice?

A. -80 °C

B. -78.5 °C

C. Other…



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Consider temperature excursions

Table 1: Headspace analysis of samples stored in freezer at -80°C for 48hrs.

Crimp	Vial A	Vial B	Vial C
Low	2000 ✓	2000 ✓	2000 ✓
Medium	2000 ✓	2000 ✓	2000 ✓
High	2000 ✓	2000 ✓	2000 ✓
Min. temp.	-80°C	-80°C	-80°C

All the tests were carried out at exactly -80°C

Small decrease in temperature caused CCI issue

Table 2: Headspace analysis of samples stored on dry ice for 48hrs.

Crimp	Vial A	Vial B	Vial C
Low	200 ✓	200 ✓	200 ✓
Medium	200 ✓	200 ✓	200 ✓
High	199/1 ✗	199/1 ✗	198/2 ✗
Min. temp.	-94°C	-88°C	-91°C

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What defects sizes can be detected with headspace analysis?

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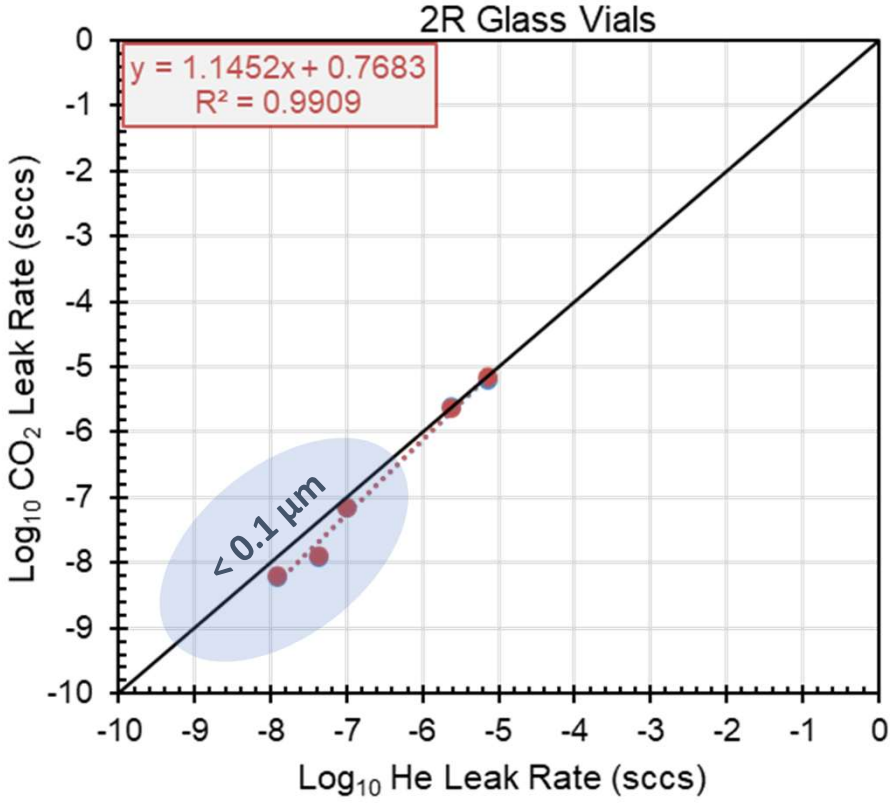
Not just (large) temporary defects…

You can detect very, *very* small leaks



*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.*

Take home message(s)

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Take home messages

- Gather lots of data on **package** AND **process**
- Gather data throughout the product life-cycle
- Use analytical techniques
- Risk of temporary leaks? Use headspace analysis

Thank you!