Headspace Applications for Container Closure Integrity

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Agenda

- **Toolbox of CCIT methods**
  - Regulatory context and Industry best practices
  - Science-based CCI data

- **Laser-based Headspace CCIT Methods**
  - Case study: Freeze dried product inspection
  - Case study: CCI during deep cold storage (-80 C to cryo)
  - Case study: Headspace Gas Ingress CCIT method

Increased regulatory attention on CCI

- Revised USP <1207> "Package Integrity Evaluation – Sterile Products" implemented in 2016
- New revision of EU Annex 1 GMP guidelines – 2nd draft made available for comment from stakeholders
- Other regulatory bodies (China, Japan for example) drafting new guidelines based on concepts in USP <1207>

Regulator: Evolution in Best Practices for CCIT

Evolution

CDER has avoided being prescriptive to allow manufacturers to develop tests to demonstrate the container closure integrity specific for their product, process, and container closure system

6

According to the regulator, the future is a **toolbox of CCIT methods.**

- Use the methods to generate science-based CCI data on the product, process, and closure system

Source: FDA CDER presentation, 2018 PDA FDA Conference, Washington D.C.

Regulator: Evolution in Best Practices for CCIT

Container Closure systems and CCIT Methods

FDA

<u>Container Closure Systems</u>

- Vials or bottles (glass and/or plastic) closed with elastomeric closures or screw-thread caps
- Pre-filled syringes or cartridges
- Flexible bags or pouches
- Blister packaging
- Packages for some drug/devices combination products

<u>CCIT Methods</u>

Probabilistic
- Dye Ingress
- Microbial ingress
- Internal Pressurization (Bubble Test)

Deterministic
- Helium Leak Testing
- Laser-based Gas Headspace analysis
- Pressure Decay
- Vacuum Decay
- Mass Extraction
- High Voltage Leak Detection
- Tracer-gas (vacuum mode)

Other
- Seal strength

2

USP <1207> describes a toolbox of analytical CCIT methods appropriate for:

- Different product configurations
- Stage in product life cycle

Source: FDA CBER presentation, 2018 PDA FDA Conference, Washington D.C.

Regulator: Evolution in Best Practices for CCIT

8.21 Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. Blow-fill-seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing. Samples of containers closed by other methods should be taken and checked for integrity using validated methods. The **frequency of testing** should be **based on the knowledge and experience of the container and closure systems** being used. **A scientifically valid sampling plan should be utilized**. The **sample size** should be **based on** information such as supplier approval, packaging component specifications and **process knowledge**. It should be noted that visual inspection alone is not considered as an acceptable integrity test method.

Draft EU Annex 1 implicitly requires scientific CCI studies to build knowledge.

How can development prepare and support manufacturing to be compliant?

What is robust science-based CCI data?

Can the data be used for:

- Making decisions about primary packaging components?
- Qualification of the container sealing process?
- Validating transport and storage?

CCI data needs to be generated in scientific studies, it is not just a quality test…

Laser-based headspace enables generation of robust CCI data.

Case study: Troubleshooting freeze dried vials in quarantine

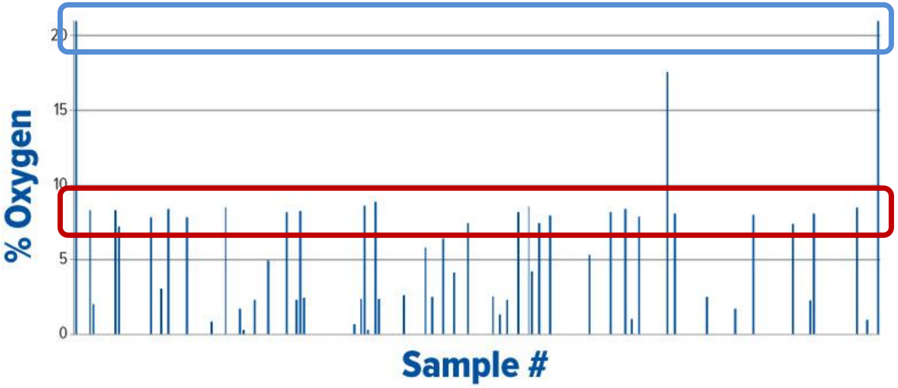
Backstory

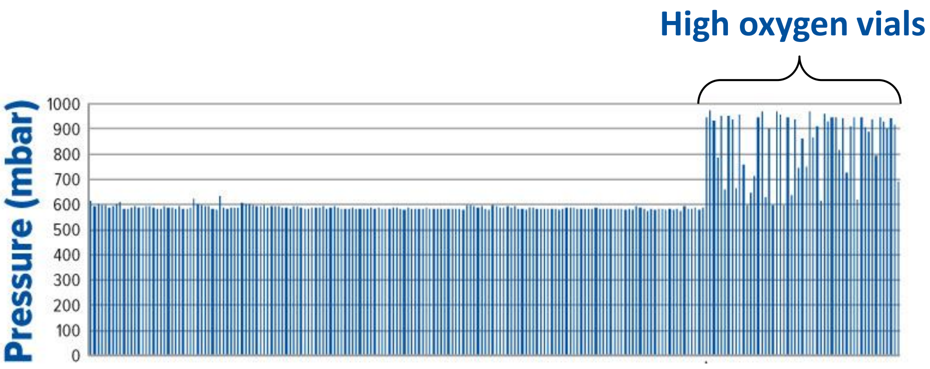
- Batch of 11,000 lyo vials placed on quarantine.
- Operators observed displaced stoppers prior to capping.
- Product stoppered at 600 mbar of nitrogen.
- Activity defined to assess risk of CCI failures due to the displaced stoppers using headspace oxygen & pressure measurements

Case study: Troubleshooting freeze dried vials in quarantine

Random Sampling

Quick analysis on a set of random samples identified high probability of CCI failure in batch

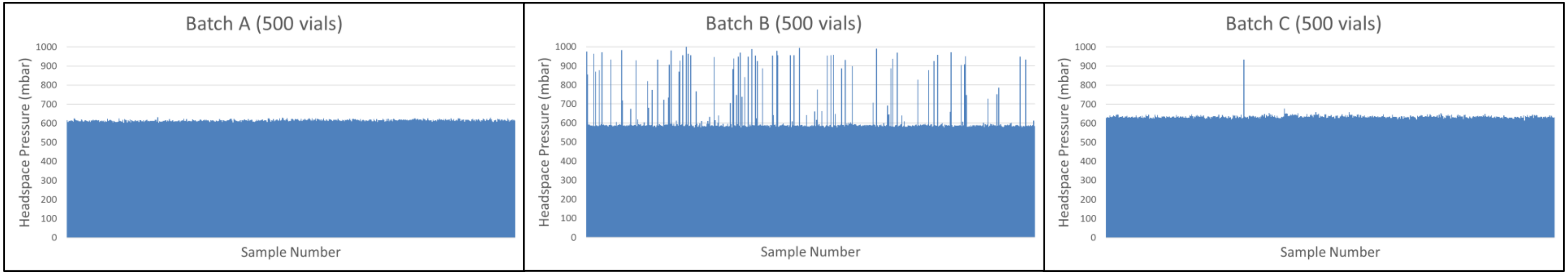




Case study: Troubleshooting freeze dried vials in quarantine

AQL Inspection

Analysis of 500 vials from three different batches revealed significant CCI failures only with quarantined batch (B)



Failure Rate: 0.0% 15.0% 0.4%

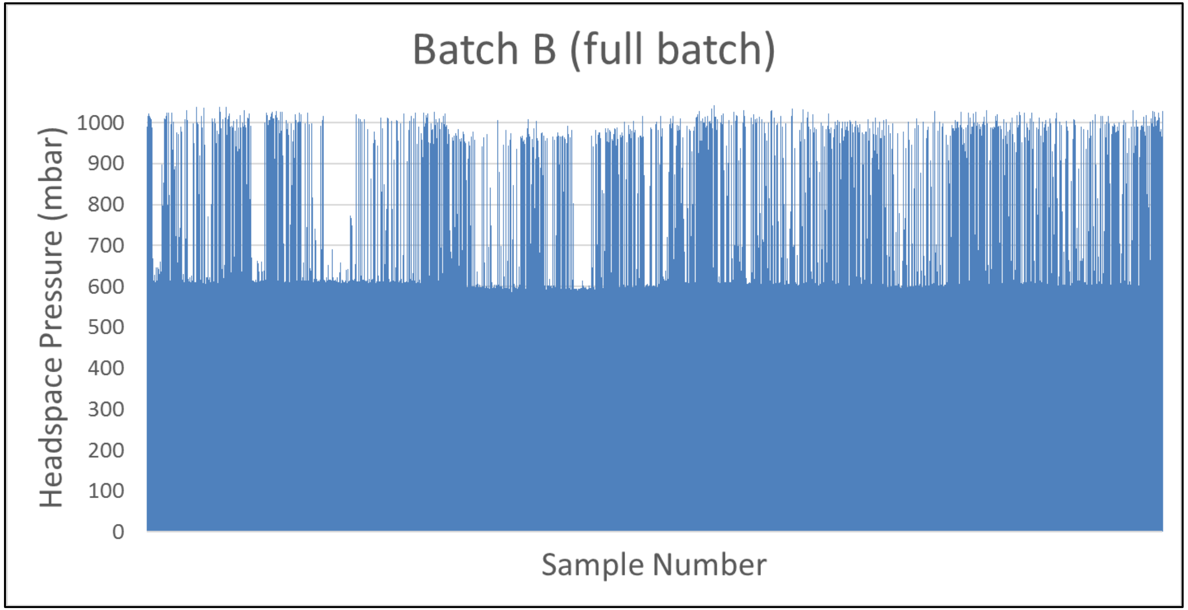
If this is happening in your lyo vial sealing process, when would you know about it?

Case study: Troubleshooting freeze dried vials in quarantine

100% Inspection

Analysis of the entire quarantined batch to identify leaked vials

Robust CCI data enabled efficient root cause analysis and assessment of risk so appropriate action could be taken



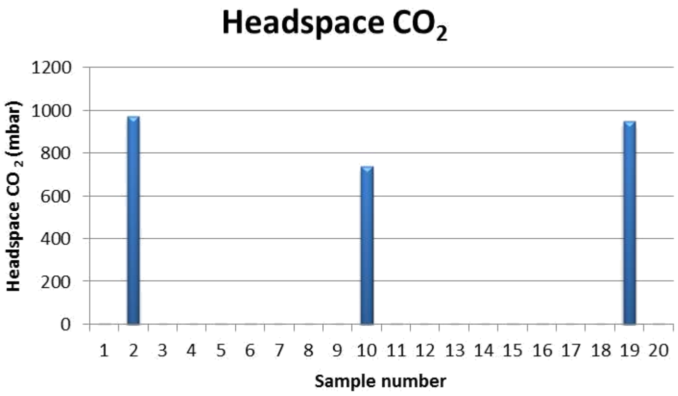
Failure rate: 16.2%

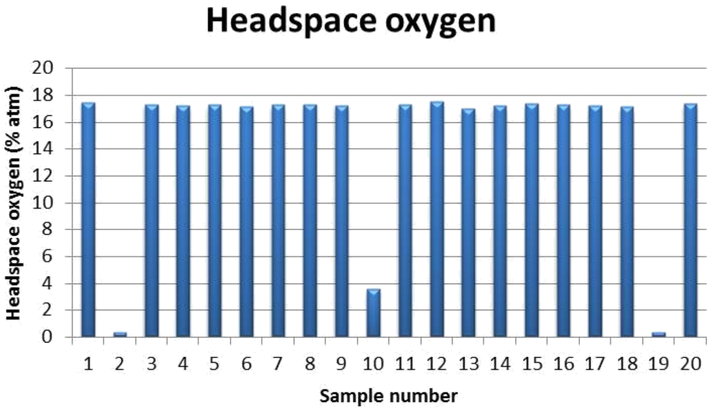
Case study: CCI during deep cold storage

- Initial headspace conditions: 1 atm of air.
- Stored on dry ice (-78.5 ˚C) for 7 days.
- Headspace conditions analyzed after cold storage.

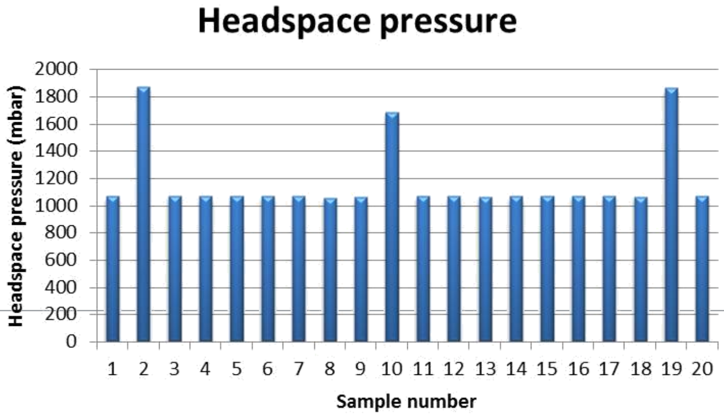
A change in headspace conditions is a direct sign that closure was lost during dry ice storage resulting in headspace gas exchange.

Case study: CCI during deep cold storage





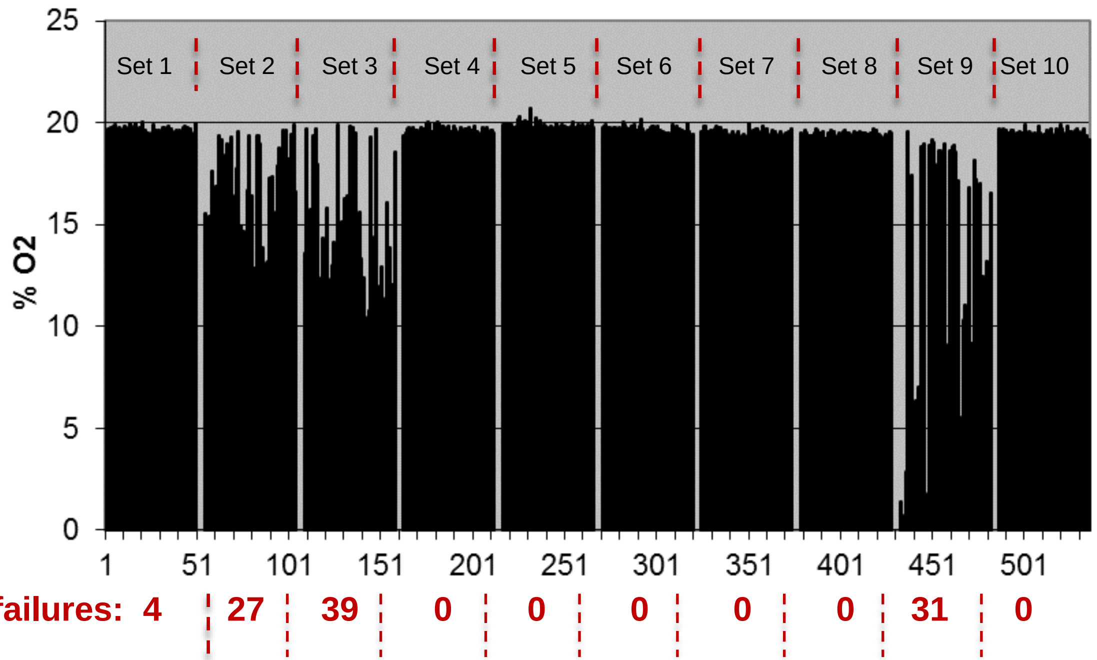
3 independent headspace measurements identify vials that lost closure on dry ice



Case study: CCI during deep cold storage

- Viral vaccine manufacturer observed vial overpressure issues in clinical product.
- Investigations were started eventually leading to CCI validation studies.
- 50 samples each of 10 different vial-stopper combinations stored on dry ice for 7 days. Headspace conditions analyzed after cold storage as a CCI test.

- **Depleted headspace oxygen levels** due to carbon dioxide ingress show certain vial/stopper combinations more appropriate for dry ice storage



REF: PDA Journal of Pharmaceutical Science and Technology 2012, 66 453-465

CCIT method survey

LIGHTHOUSE conducted a survey in Spring 2020 with > 100 pharmaceutical contacts involved with CCI testing:

- 70% responded that they use blue dye ingress in CCIT activities.
- Each of the deterministic CCIT methods described in USP <1207> received a score of ~ 20% current usage in CCIT activities.
  - Vacuum decay, pressure decay, helium leak, HVLD, laser-based headspace gas analysis

The results of this survey indicate that the industry is slowly replacing the blue dye test with an equal implementation of the deterministic methods (toolbox approach) since the implementation of USP <1207> in 2016.

Blue dye ingress test

- Most common CCIT method used today
- Regulators requiring more robust method validation data

Bottom Line:

- Spectrophotometric Detection
- Limit of Quantitation for Instrument
- Positive Controls which adequately demonstrate the test conditions can cause an appropriate leak
- Test of Appropriate Sample (sterilization conditions, sample type)
- Appropriate Test Condition (Pressure and Vacuum, time, dye concentration)
- Positive control vial fashioned near LOQ to indicate that the spectrophotometer is working correctly

11

Source: FDA CVM presentation, 2018 PDA FDA Conference, Washington D.C.

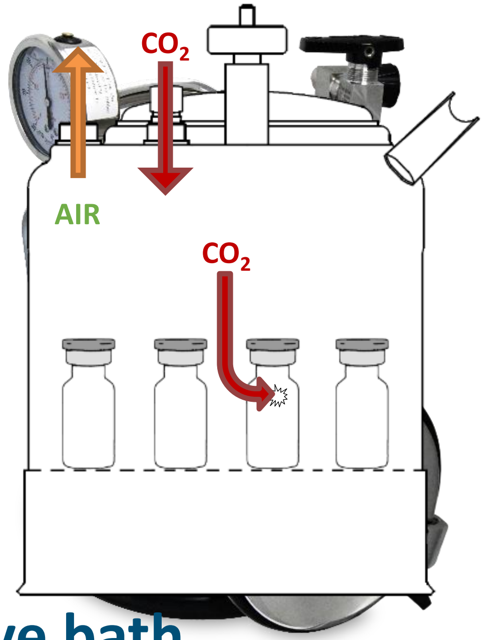
Requirements for a science-based CCIT approach

- Sensitive enough to detect critical leaks.
- Capable of generating analytical data (remove human subjectivity).
- Ability to generate statistical data.
- No impact on product (non-destructive).
- Easy to use, straightforward to validate.

Headspace Gas Ingress Testing for CCI

Objective

- Develop a headspace approach similar to blue dye but better
- Method must be non-destructive, generate analytical data, reliably detect critical leaks, be straightforward to validate



Headspace Gas Ingress Test Method

- Samples placed in CCI Test Vessel
- Vessel pressurized with X bar of CO_2 for Y min
- Samples removed and tested for headspace CO_2

Samples exposed to a gas bath instead of blue dye bath

Headspace Gas Ingress Testing for CCI

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- **Positive control set**: 5 µm laser-drilled defect located 20.75 mm from bottom of 15R vial
  - T0 measurement verifies initial headspace CO_2 is zero
  - T1 measurement after 30 min storage with 2 atm CO_2

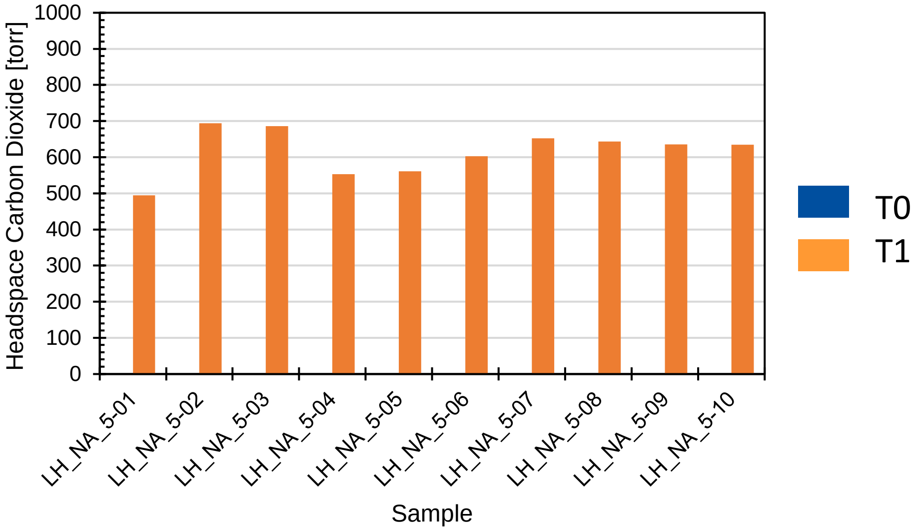
1. Positive controls
2. Samples put in CCIT vessel
3. Samples analyzed for headspace CO_2

Headspace Gas Ingress Testing for CCI

- Gas ingress testing using CO_2 overpressure easily identifies 5 micron positive controls.
- Positive control vials show almost 1 atm headspace gas exchange (600 – 700 torr of CO_2).

Robust CCIT method development and validation can be done with this approach – what the regulator wants.

Results for 5 µm laser-drilled defects



Summary: Headspace Gas Ingress Testing for CCI

Blue dye test

- Ingress of methylene blue
- Qualitative visual inspection
- Destructive method
- Useful for gross leak detection

Methylene blue:
$C_{16}H_{18}N_3SCl$

Headspace gas ingress test

- Ingress of CO_2
- Analytical measurement
- Non-destructive method
- Sensitive to all leak sizes
- Described by gas flow physics *

Triatomic gas molecule: CO_2

* PDA Journal Nov-Dec 2017 issue (71): Method Development for CCI Evaluation via Gas Ingress by Using Frequency Modulation Spectroscopy [K. Victor]. p 429-453

Conclusions

- **CCI testing is not just a verification test**
  - A toolbox of methods is needed appropriate for products/processes.
  - Methods should enable (statistical) science-based data (i.e. for qualification of closure systems, container sealing processes, transport and storage).

- **Laser-based Headspace CCIT Methods**
  - Headspace methods enable CCIT of product having increased risk of CCI issues (i.e. lyo product, deep cold storage product).
  - A general Headspace Gas Ingress method can replace blue dye ingress testing.

Parenteral Drug Association

THANK YOU!

For further QUESTIONS and FEEDBACK on the material in this presentation, please feel free to contact me:

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