Laser Based Headspace Analysis for CCIT

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Overview

Part 1: Theoretical background

- How does gas ingress work?
- How can theory be applied?

Part 2: Case studies

- Application to CCI testing - products packaged under a modified atmosphere
- Method development and validation lyo products
- 100% inspection of lyophilized product

Part 3: Case studies

- Application to CCI testing - products packaged under a non-modified atmosphere
- Filling line CCI qualification
- Cold Storage CCI Study

Part 1

Theoretical background

Gas ingress for CCI testing

- Two different ways by which gas can flow through a defect in and out of a pharmaceutical container:

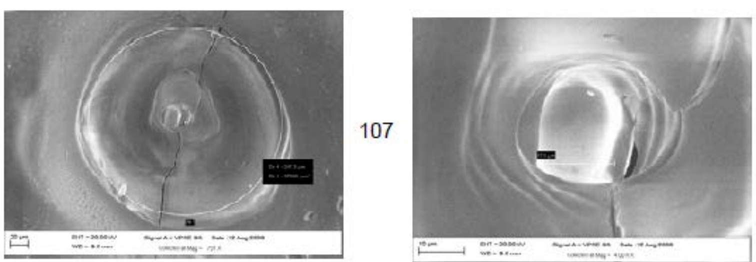
- **Effusion**: gas flow generated by a total pressure difference across the container defect

- **Diffusion**: gas flow of a particular gas generated by a partial pressure difference of that gas across the container defect

Understanding this gas flow enables the development of CCI test methods based on the measurement of gas ingress

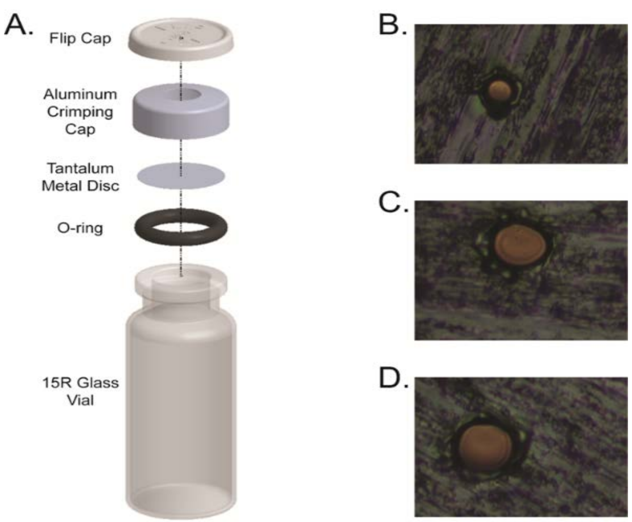
Positive controls – validating headspace gas ingress methods

- CCIT methods based on detecting gas ingress into the headspace can be demonstrated and validated using known positive controls
- Gas flow physics model also enables calculation of test method sensitivity



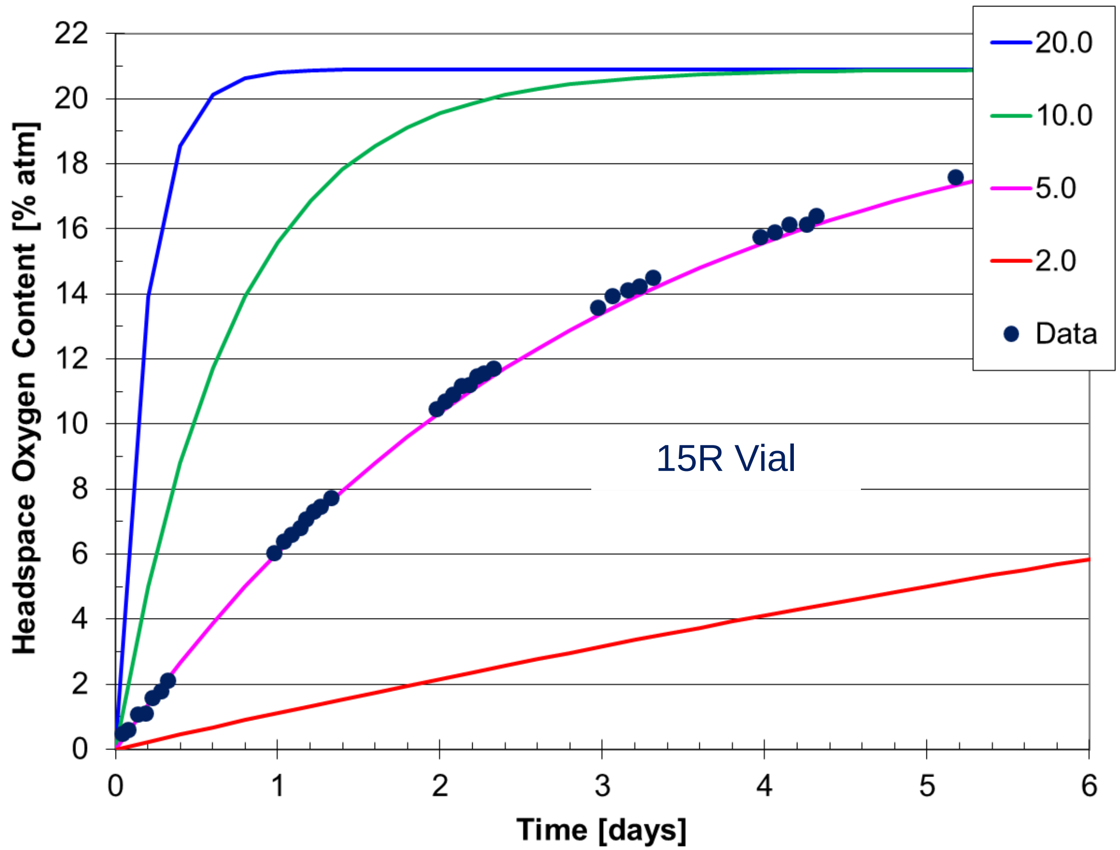
Nominal hole size 5 µm

Image provided by Lenox Laser



Oxygen Ingress Model Example

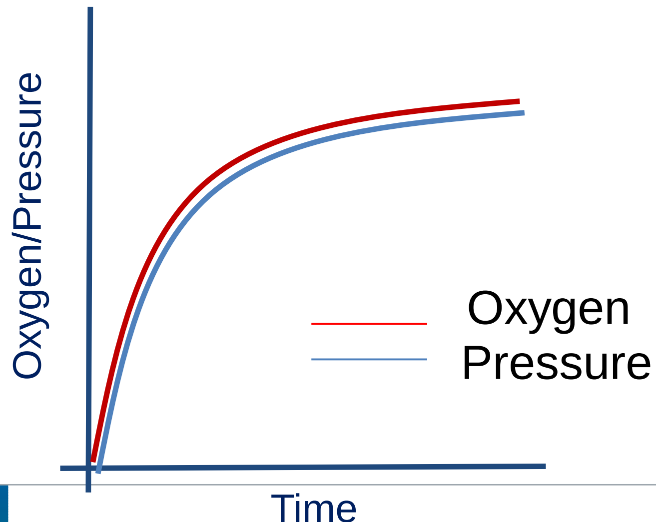
Predicted oxygen concentration versus time for **ideal defects**



Defect diameter [µm]

Published in 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.

CCI testing-products packaged under modified atmosphere



Product

- Lyophilized product:
  Partial vacuum with nitrogen or full vacuum
- Oxygen sensitive liquids:
  Purged with nitrogen

Storage Condition

- Ambient air

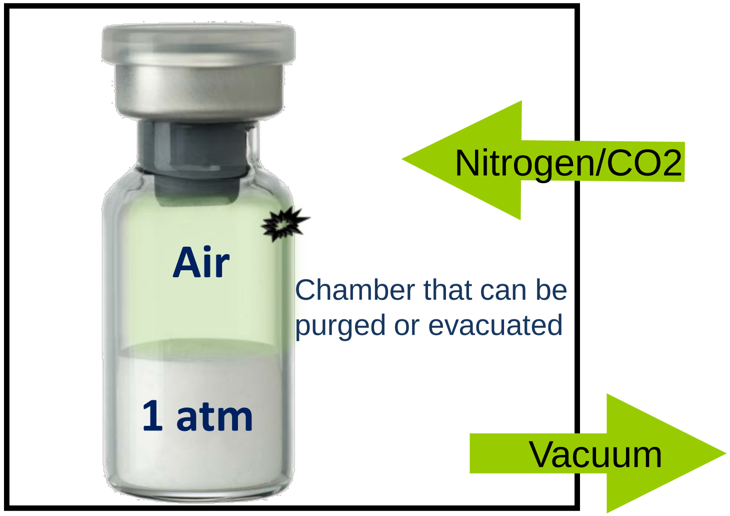
Leak Indicating Measurement

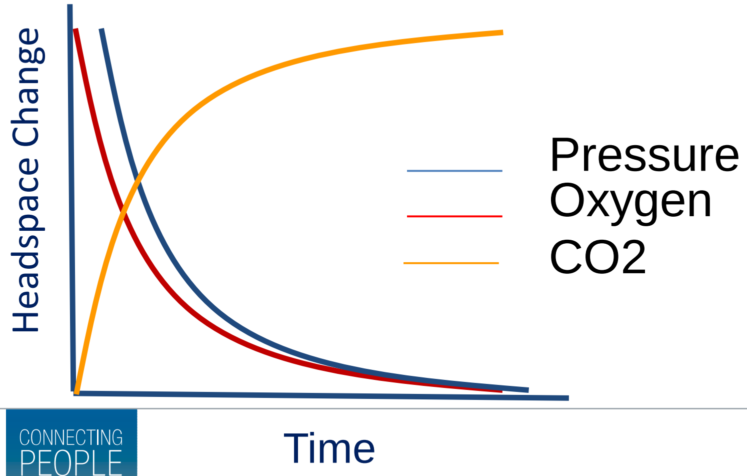
- Increase in oxygen level and/or increase in pressure.

Application

Laboratory instruments or automated inspection

CCI testing-products packaged under a non-modified atmosphere





Product

- Headspace is air at 1 atm
  Typical of many liquids

Storage Conditions

- Samples put in a chamber to drive a headspace change
- After pre-determined conditioning time, remove samples, test in a headspace analyzer.

Leak Indicating Measurement

- Decrease in oxygen level OR increase in tracer gas (CO2)

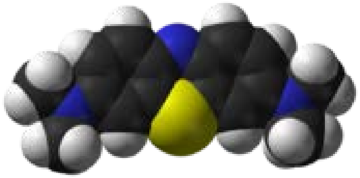
Application

Laboratory instruments

Headspace gas ingress as CCIT method

Blue dye test

- Ingress of methylene blue
- Qualitative visual inspection
- Destructive method
- Permanent leaks
- Useful for gross leak detection, CCI verification



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

Laser-based headspace

- Ingress of O_2 , N_2 and/or CO_2
- Analytical measurement
- Non-destructive method
- Permanent *and* temporary leaks
- Sensitive to all leak sizes
- Quantitatively described by gas flow physics

Diatomic gas molecule

Similar to blue dye but much more sensitive, can be validated as an analytical method (ICH Q2(R1)), can be used in all stages of the product life cycle

Headspace Analysis Systems

Laboratory and At-line Instruments and accessories

Automated Inspection Machines

BOSCH
Invented for life

Strategic partnership with Bosch for CCI machines with Lighthouse laser measurement technology inside.

Part 2

Case studies – modified headspace

Case Study 1: Method development and validation – lyo product

- Headspace analysis CCI method development and validation based on USP<1207>
- Data & reports reviewed and approved by FDA

Overview of Project

1) Information gathering
   - Product picture, feasibility assessment, type and size vial, headspace composition, # and sizes positive controls, etc.

2) Method Development project at Lighthouse
   - Verify initial headspace conditions, predict headspace changes using validated leak rate model, design protocol, perform tests

3) On-site system and Method Validation
   - Lighthouse headspace system IQ/OQ & 21-CFR-11
   - Provide Method Validation Protocol according to USP<1207> and ICH Q2/R1 guidelines

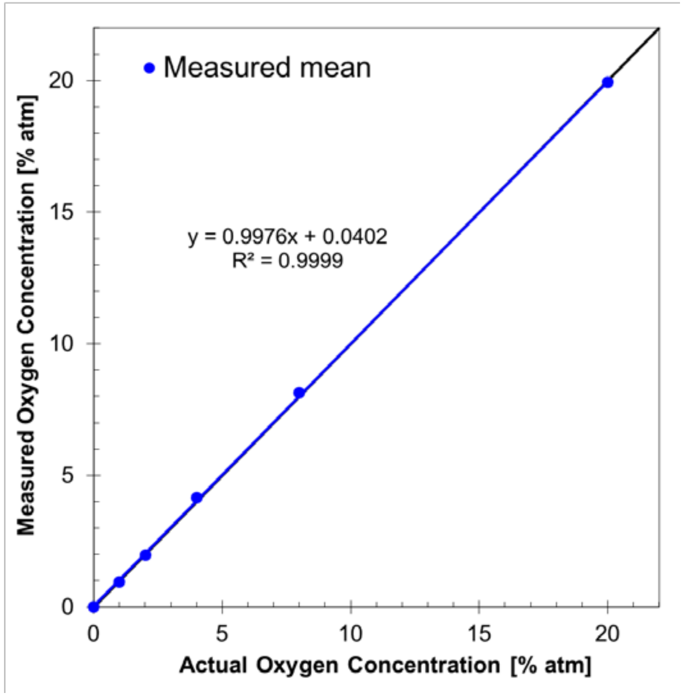
Case Study 1: Method development and validation – lyo product

Measurement Performance:

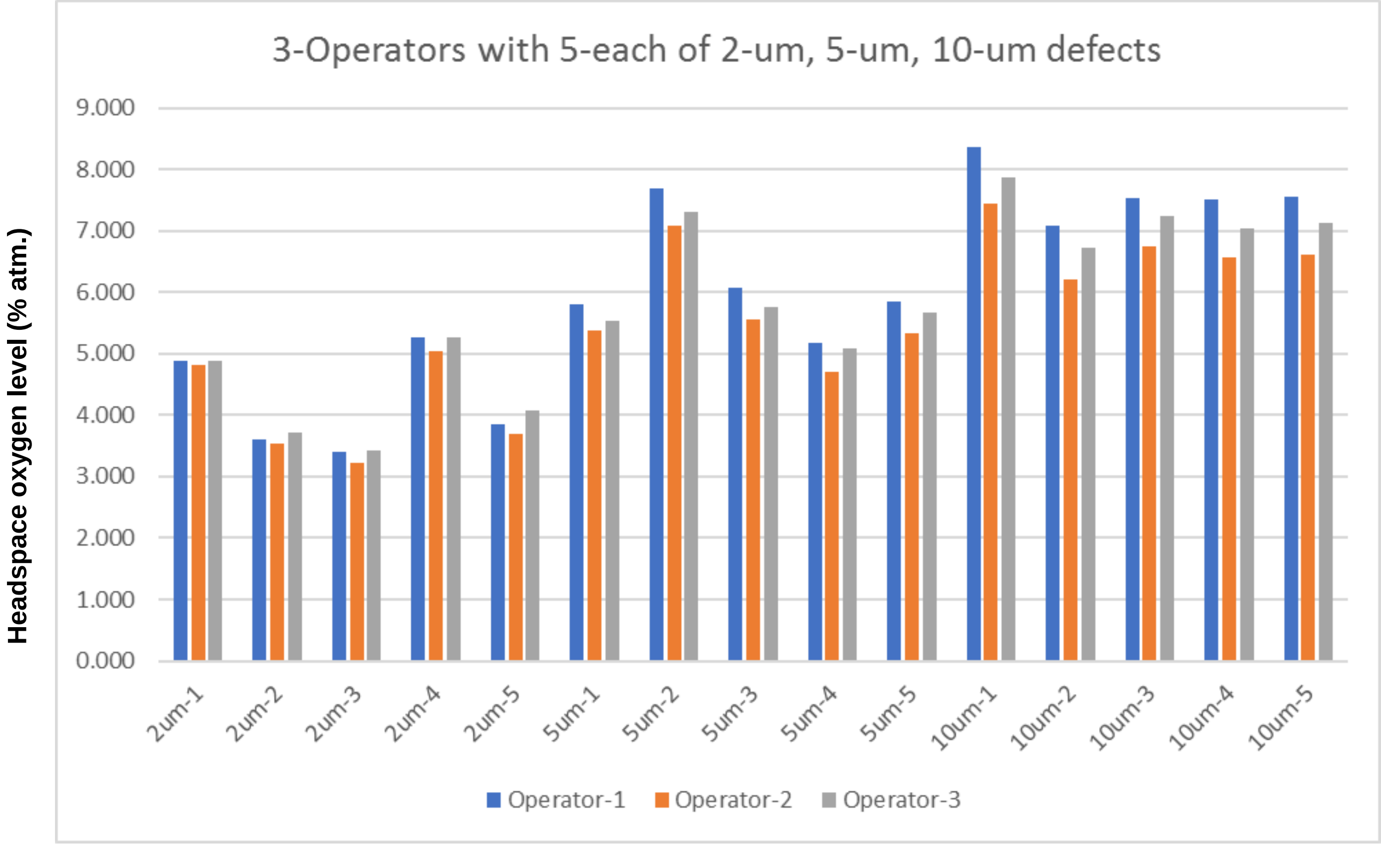
Instrument and machine qualification using NIST traceable standards.

N=100	Headspace Oxygen (% atm)			
Standard Label	Known Value	Meas. Mean	Error	St. Dev.
0.0	0.000	0.01	0.01	0.02
1.0	1.005	0.96	-0.04	0.03
2.0	2.004	1.98	-0.03	0.03
4.0	3.998	4.02	0.02	0.04
8.0	7.999	8.13	0.13	0.03
20.0	20.00	19.93	-0.06	0.04

↑ Accuracy (Error) ↑ Precision (St. Dev.)



Case Study 1: Method development and validation – lyo product



Each operator tested all 15-positive controls

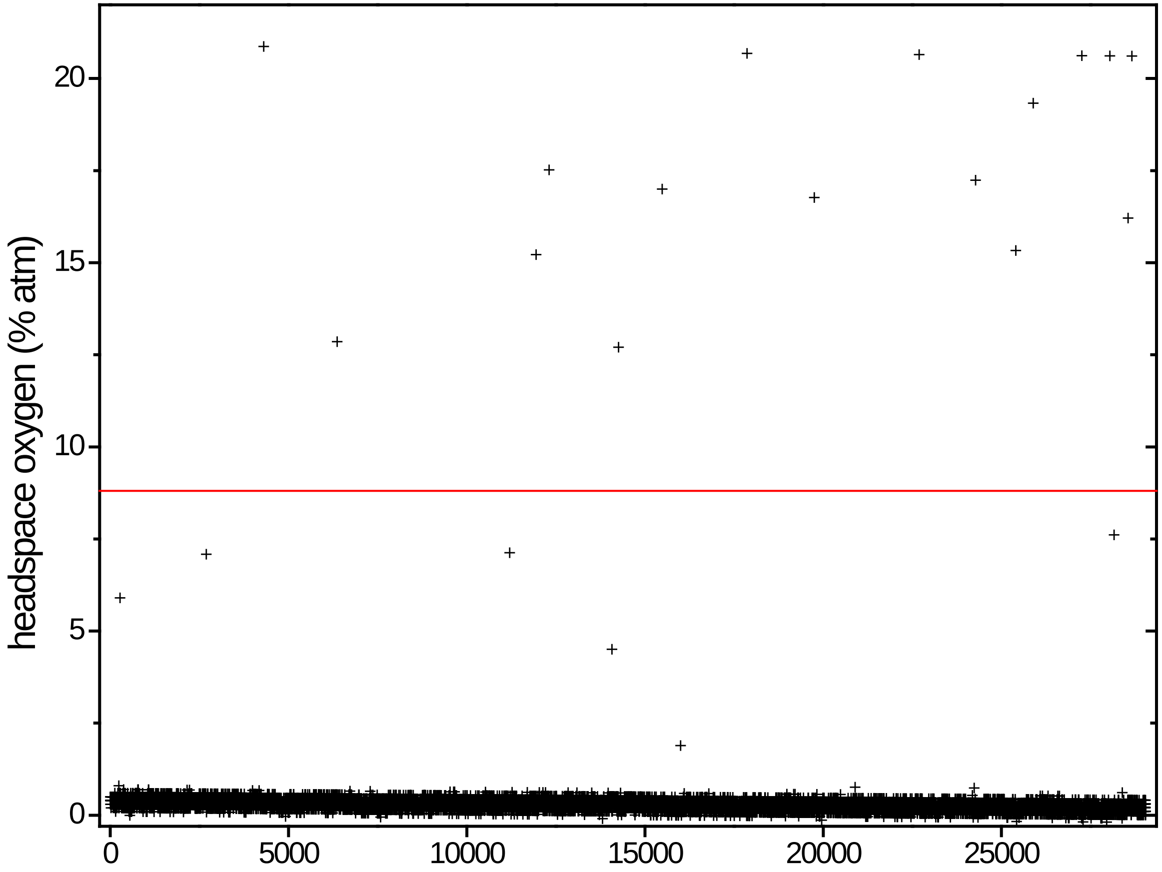
100% of defective vials were detected

Case Study 1: Method development and validation – lyo product

CCI Validation Overview of Results

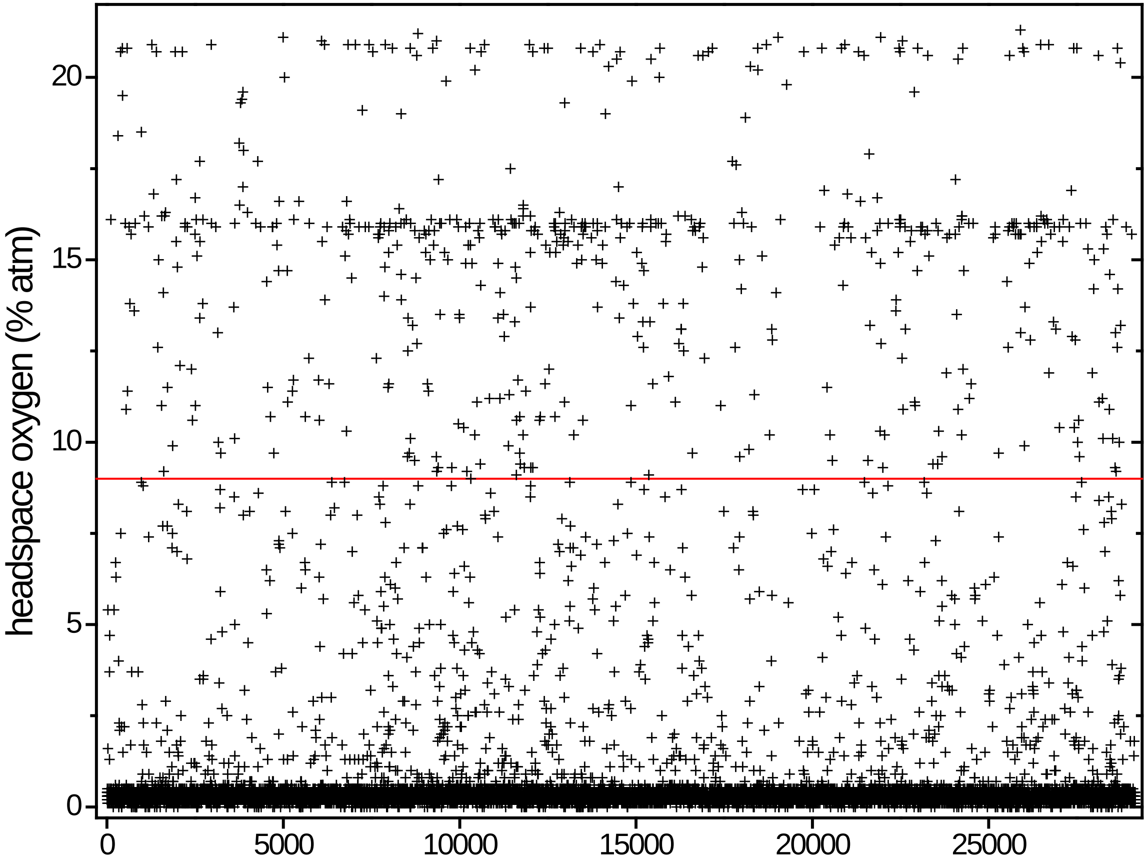
	Operator-1	Operator-2	Operator-3
2um Defect 5-vials	5 of 5 100%	5 of 5 100%	5 of 5 100%
10um Defect 5-vials	5 of 5 100%	5 of 5 100%	5 of 5 100%
20um Defect 5-vials	5 of 5 100%	5 of 5 100%	5 of 5 100%
Gross Defect 5-vials	5 of 5 100%	5 of 5 100%	5 of 5 100%
No Defect	0 of 5 100%	0 of 5 100%	0 of 5 100%

Case Study 2:
100% Inspection of lyo product



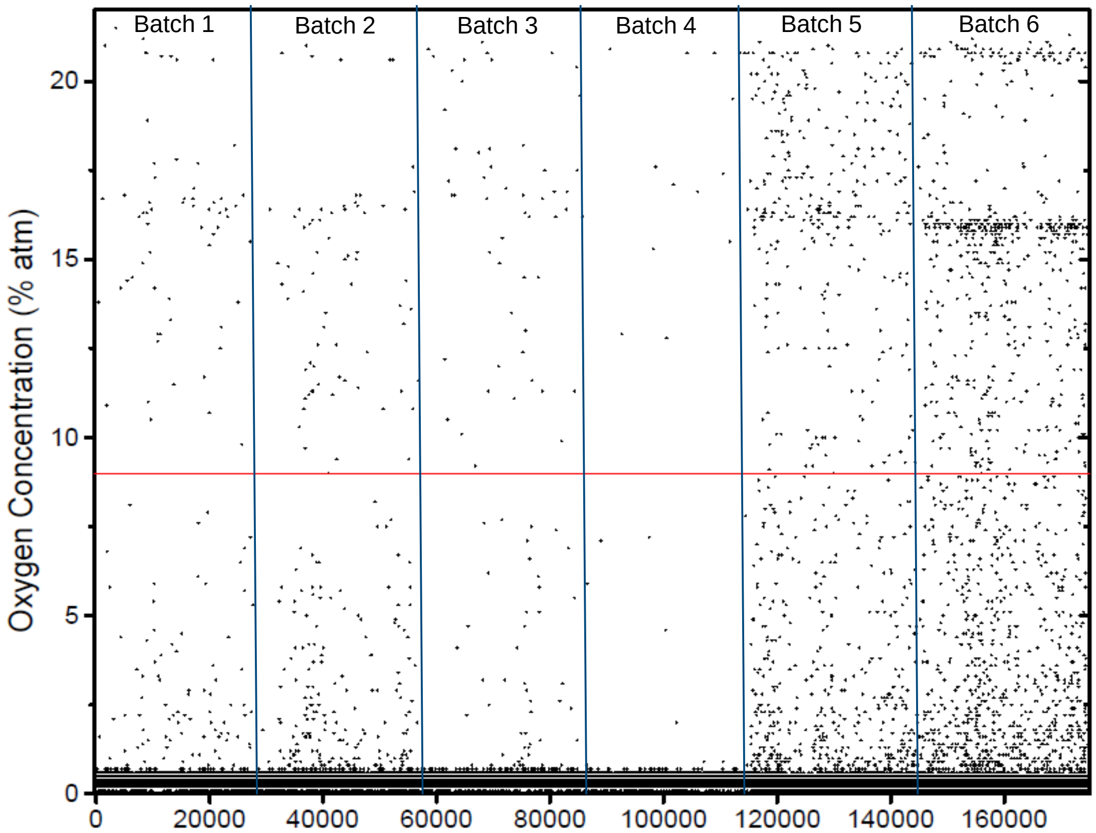
Total batch size: 29048
Number rejected: 16
Reject rate: 0.06%

Case Study 2: 100% Inspection of lyo product



Total batch size: 29156
Number rejected: 568
Reject rate: 1.95%

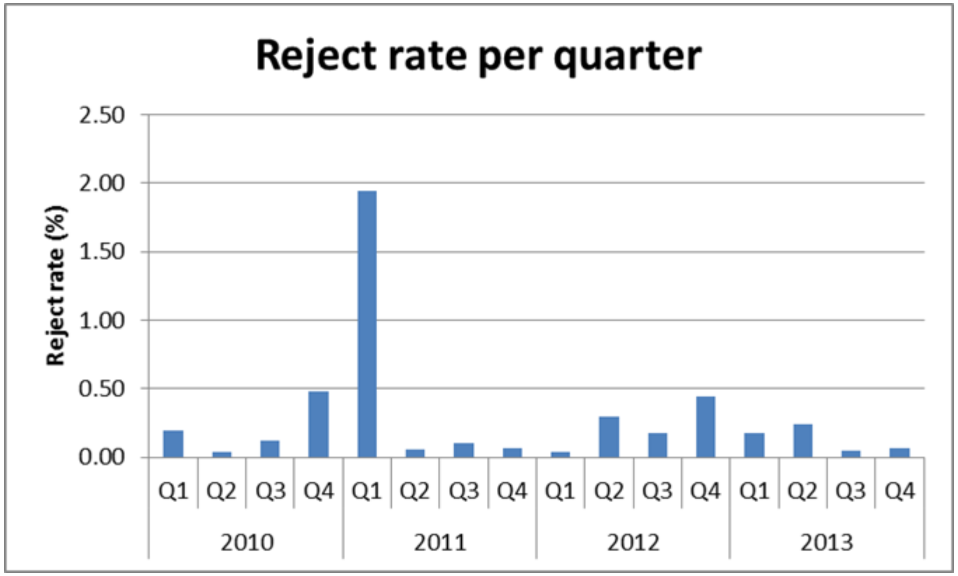
Case Study 2:
100% Inspection of lyo product



Results of 6 chronological batches

Not a robust process

Case Study 2:
100% Inspection of lyo product



Case 100% inspection

4 years of manufacturing data:

- 156 lots
- Total 1.6 million vials

Results

44-lots (28%) with zero rejects

3-lots had > 2% reject rate

Average reject rate was 0.27%

It is difficult to manufacture a perfect batch

Part 3

Case studies – non-modified headspace

Case Study 3: Filling line CCI qualification

Objective: Qualify that the filling process produces good CCI for a specific vial-stopper combination

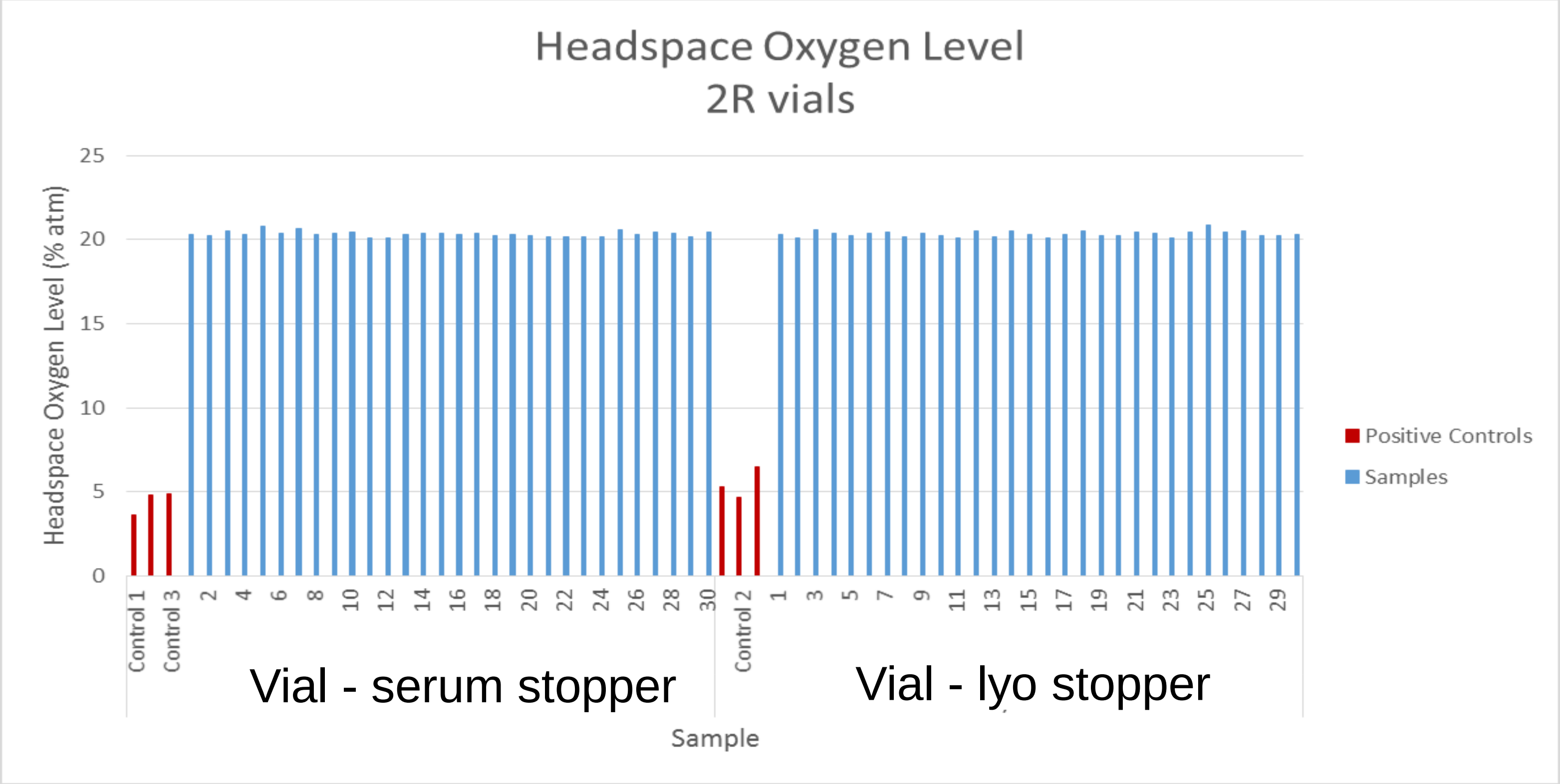
CCI Study:

- Produce empty stoppered & crimped vials with the process. Initial headspace is 1 atm of air (20.9% oxygen).
- Use headspace gas ingress model to design a sample chamber evacuation, nitrogen backfill, and sample hold cycle.
- Measure samples for changes in headspace composition. Include positive controls having a 10 µm micro-capillary through the stopper.

	Headspace Oxygen Level after defined evacuation, backfill, and storage cycle [% atm]		
Sample Vial	1 µm ideal defect	0.6 µm ideal defect	0.5 µm ideal defect
2R	1	4.1	7.1
6R	3.4	12.1	15.0
20R	11.1	18.8	19.5

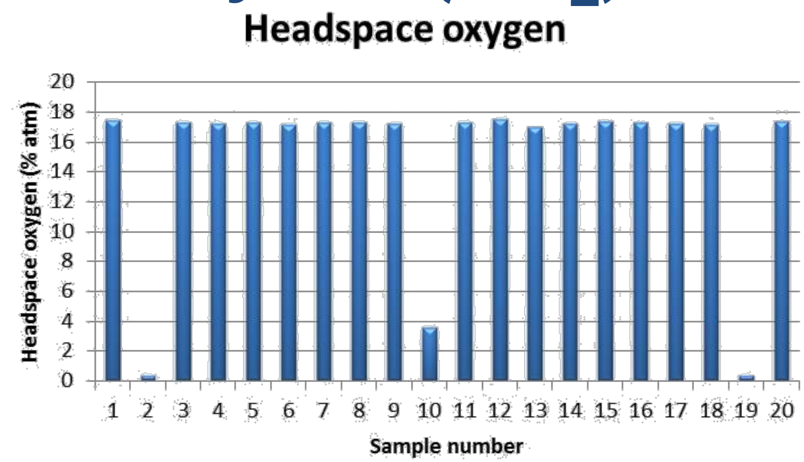
Case Study 4: Filling line CCI qualification

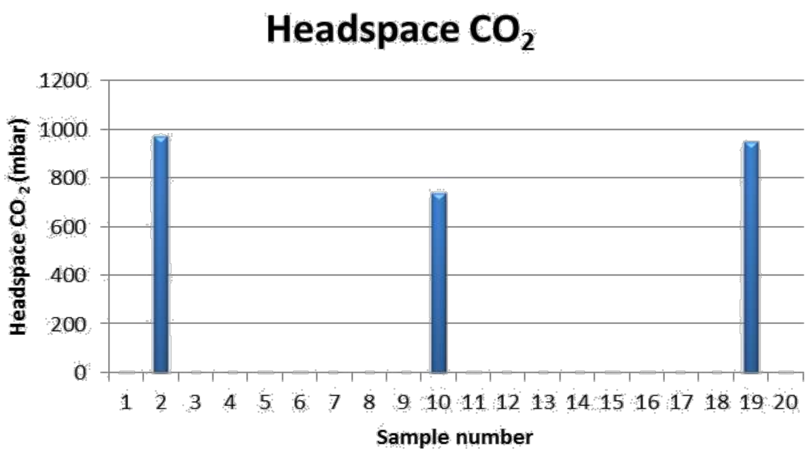
Results headspace CCI test



Gas ingress measurements produced robust CCI qualification data

Case Study 5: CCI testing for vials stored on dry ice (CO_2)





Case

- Air headspace vials stored on dry ice (CO_2)
- Storage on dry ice increases risk of CCI loss
- Conventional rubber stoppers lose elasticity at -80°C risking CO2 ingress

Result

- 3 containers revealed decreased oxygen levels
- Same vials revealed increased CO_2 levels

Thank you!