Container Closure Integrity Testing (CCIT) Datasheet

Features

Pharmaceutical and some food products are expected to be free from microbial contamination and safe to use right from production throughout their shelf-life, but different products and container types necessitate different testing methods according to their content, material of packaging, design and regulatory requirements.

Container Closure Integrity Testing (CCIT) (USP <1207>), commonly referred to as leak detection, is a non-destructive packaging inspection system to maintain an aseptic barrier against potential contaminants. Is a deterministic testing procedure, so it is less subject to error, is repeatable and gives quantitative and predictable results.

Why Container Closure Testing is important:

CCIT detects defects that demonstrate breach of the container and/or closure system.

Patient and consumer health and safety is the principal reason why testing methods are put into place. Product sterility and consumer safety begins at the product development phase by evaluating the suitability of primary packaging in its ability to offer a sterile barrier thanks to its container closure system which should not result in contamination or leaks of the drug or product.

The United States Pharmacopeia (USP) and Food and Drug Administration (FDA) impose strict requirements for Container Closure Integrity Testing (CCIT).

As per the 21 Code of Federal Regulations (CFR) part 211.94, container closure systems must provide adequate protection against anticipated external factors in storage and use, that can cause deterioration or contamination of the drug product. It also establishes the standards or specifications and methods of testing in the validation procedures.

The leak detection guidelines establish that container security testing methods should use analytical detection techniques appropriate to the method and compatible with the specific product being tested. Validation of methods should be specific to the product container and closure system or product type.

How the CCIT method works:

- Common CCIT methods:
- Vacuum Decay Method
- Pressure Decay Method
- Lid Deflection
- Force Decay
- Headspace Gas Analysis (HGA)

How the CCIT method works:

The method of CCIT chosen will vary according to the desired result like the leak rate measurement of the entire container, potential for microbial ingress, detection of presence of leak paths etc.
Container Closure Integrity Testing Method requires the creation of positive and negative controls, taking into consideration the design, material, expected package leak features and content. This is done to mimic defects and is inspected together with the intact samples.
Laser drilled holes is one of the ways in which Positive controls can be created. With laser drilled hole simulation, the sample geometry remains intact and the simulation resembles the natural defects in glass (cracks) and polymers (micro holes), as leaks that occur naturally are likely to be meandering paths and not to perfect holes. The size of the simulated leak in the laser-drilled hole requires calibration.
Other than the leak test method and positive and negative sampling, which should be sufficient enough to provide adequate assurance of package integrity (USP <1207.1>), the criteria for acceptance must also be determined and accordingly all negative controls should pass while all positives must fail. A lower and an upper limit of detection should also be established, followed by a validation protocol that highlights the parameters established during the process. Validation is essential to prove test method precision (demonstrating repeatability), accuracy (correctly identifying leaks), and detection limit. In case of modifications in package design and material or processing the CCIT method should always be re-evaluated too for ensuring patient and consumer safety.

Closure Integrity Test

Container closure integrity test methods

The USP <1207> chapter provides an overview of CCI testing technologies and categorizes them as being deterministic or probabilistic (see Table 1 below). The chapter emphasizes that this overview of CCI testing technologies is not exhaustive but is a summary of technologies that have been implemented for CCI testing in the pharmaceutical industry and that are described by a body of peer-reviewed literature.

Deterministic	Probabilistic
Electrical conductivity and capacitance (*high voltage leak detection*)	Bubble emission
Laser-based gas headspace analysis	Microbial challenge, immersion exposure
Mass extraction	tracer gas detection, sniffer mode
Pressure decay	Tracer liquid (*blue dye ingress*)
Tracer gas detection, vacuum mode	
Vacuum decay	

Dye Ingress Testing :

Sample and positive control packages are fully submerged in a dye bath. A vacuum pressure of about 0.5 atmospheres is applied for a specific amount of time, samples are returned to atmospheric pressure, and then a positive pressure of about 2 atmospheres may be applied for a specific amount of time. The packages are then visually compared to a sensitivity solution of a known concentration of dye to evaluate the samples for the presence of dye inside the packages. Alternatively, the solutions inside the packages can be tested for the presence of dye using a UV/Vis spectrophotometer.

Microbial Immersion Testing

Generic in-house methods are available and may be customized based on individual testing requirements. Techniques offered include Vacuum, Static, or Challenge Organism.

Microbial Aerosol Challenge Testing

Generic in-house methods are available and may be customized based on individual testing requirements. Techniques offered include Vacuum, Static, or Challenge Organism. Vacuum or Static techniques utilize a 0.4 m3 air-tight test room connected with thermo-stated aerosol delivery system

Deterministic Methods :

Vacuum Decay
Description: Measures leaks by vacuum decay based upon ASTM F2338. Performs leak testing with sensitivity to detect leaks down to approximately 5 microns. This option reduces the amount of valuable finished drug product required for stability testing as the testing is non-destructive to the sample, and therefore, the same sample can be used for other laboratory tests typically required during stability studies once the vacuum decay test has been performed.
Best Application: This technology is suitable for leak testing on container/closure systems such as syringes and vials. Because this method is non- destructive to the sample under test, it is a great option for leak testing both before and during stability studies.

Pressure Decay
Instrumentation: TM Electronics BT Integra Burst, Creep and Leak Tester
Description: Measures leaks by pressure decay based upon ASTM F2095.
Best Application: This technology accommodates both seal and package integrity testing for flexible packaging, such as bags and pouches. This is a destructive test.

High Voltage Leak Detection
Instrumentation: E-Scan 655 Micro Current High Voltage Leak Detector (HVLD)
Description: Detects package defects using an electrical current.
Best Application: This technology is suitable for use with liquid-filled parenteral drug product glass vials and syringes, where the packaging is far less conductive than the liquid inside.

Oxygen Headspace
Instrumentation: FMS-760 Oxygen Headspace Analyzer
Description: Uses Frequency Modulation Spectroscopy (FMS) to detect oxygen in the headspace of transparent rigid containers and measures rise or fall in the oxygen levels in the container's headspace to identify a potential leak. It can also be used to determine the rate of oxygen permeation into a sealed container over time.
Best Application: Because this method is non-destructive to the sample under test, it is a great option for leak testing parenteral containers both before and during stability studies. This technology is also used during package development to verify inherent package integrity and maximum allowable leakage limit (MALL) through leak rate modeling.

Helium Leak Detection
Instrumentation: Helium Mass Spectrometer - Tracer, Gas Detection, Vacuum Mode
Description: Quantitates the flow rate of helium from leaks in packaging after having been flooded with helium as a tracer gas. If a defect is present, the helium is then drawn out of the packaging through the defect by vacuum and detected using a mass spectrometer. This method is the most sensitive option, allowing for the detection of defects as small as 0.2 microns.
Best Application: This technology is suitable for package development to verify inherent package integrity and maximum allowable leakage limit (MALL). This technique is applicable to a wide variety, of package types, can isolate and identify leak location, and can directly measure leak flow rates.

USP <1207.1>
Leak Detection Index

	Detectable Leaks	
Limit of Detection Index	Air Leak Rate (std cc/S)	Orifice Leak Size (um)
Class-1	$<1\ 10^{-6}$	<0.1
Class-2	10^{-6} to 10^{-4}	0.1 to 1
Class-3	6×10^{-4} to 4×10^{-3}	2 to 5
Class-4	5×10^{-3} to 1.6×10^{-2}	6 to 10
Class-5	0.017 to 0.360	11 to 50
Class-6	>0.360	>50

USP <1207.2>
Leak Detection Summary

	Leak Detection Class	Measurement Outcome
Tracer-gas	Class 1-4	Helium Loss
Laser-Headspace	Class 1-6	Gas Composition or Gas Pressure
HVLD	Class 3-6	Electrical Current
Pressure Decay	Class 3-6	Pressure Drop
Vacuum Decay	Class 3-6	Pressure Rise
Mass Extraction	Class 3-6	Mass Flow

Characterizing the headspacenon-destructively

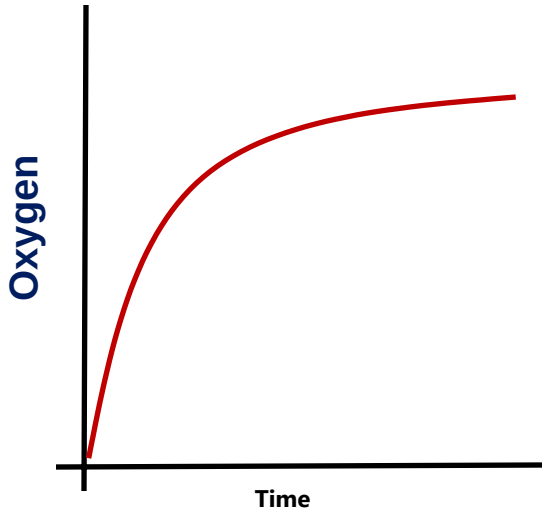
Laser light matches frequency of target molecule.

Amount of absorbed laserlight is dependent on concentration of target molecule in headspace.

What gases can be measured?

- Headspace oxygen
- Headspace carbon dioxide
- Headspace moisture (water vapor)
- Headspace total pressure levels

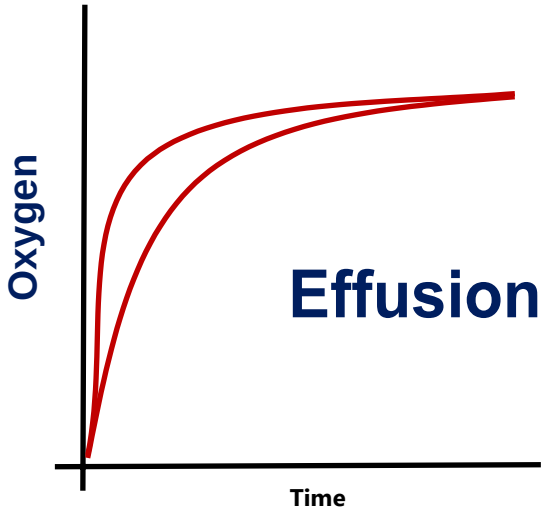
CCI testing – how?

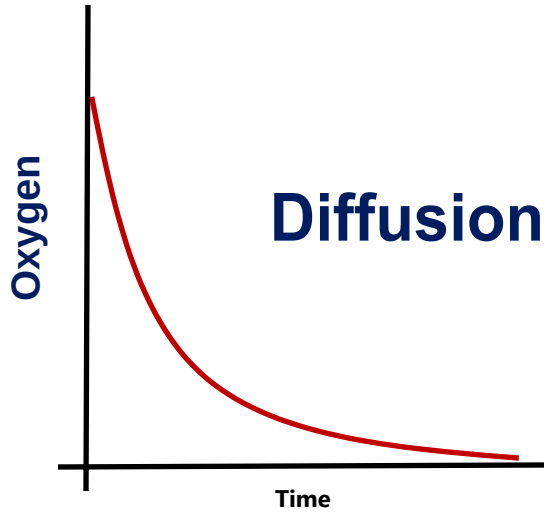


Headspace Measurement

Exchange of gas between the container and the outsideenvironment through a defect

CCI testing: other situations





What type of product-packages?

- Sterile liquid, or lyophilized, ordry-powder filled
- Transparent rigid containers:
  - Clear or amber glass
  - Transparent plastics
- Vials, syringes, ampoules, cartridges
- Nominal volume ranging from0.2mL to 250mL

Advantages & disadvantages

Advantages	Disadvantages
• Non-destructive	• Not all fill levels
• Rapid	• Sample needs to betransparent to laser
• Quantitative results	• Inline production inspection needs modifiedheadspace
• Deterministic method	
• Operator independent	
• Applicable over whole leakrange	
• Permanent & temporary leaks detectable	

Equipment

Assembly : Fig.1

Stainless Steel Vessel 5ltr Capacity , Made od ss316 l with oil free vacuum & pressure pump with vacuum tube

Assembly : Fig.2

CCK Stainless Steel Vessel Test tube Stand Rack (Customize available) On request

Assembly : Fig.3

For perfect monitoring Vacuum/ Pressure Gauge

Assembly : Fig.4

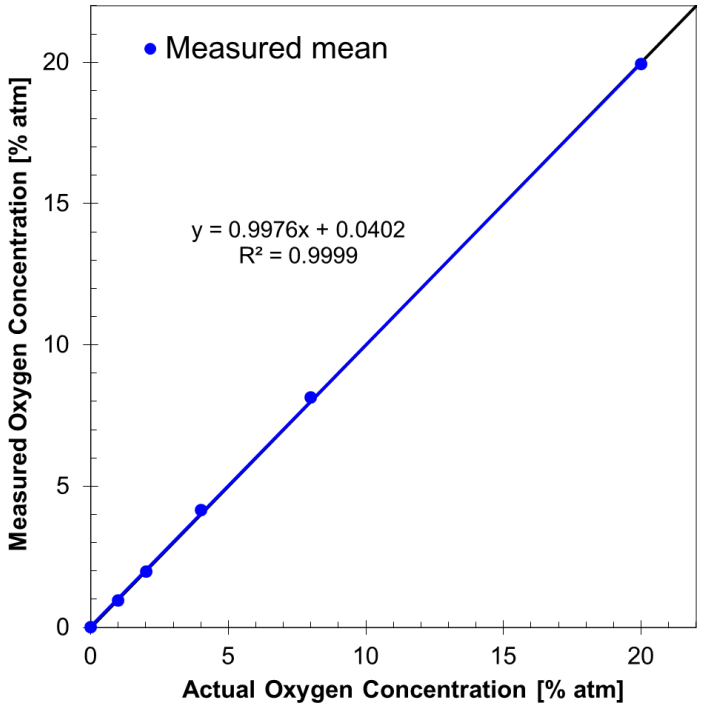
Available 5 ltr & 10ltr

Measurement performance

N=100	Headspace Oxygen (% atm)			
StandardLabel	**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

Precision



Note :

Part 2

GAS DIFFUSION THEORY

CCI testing: Gas diffusion theory

$$\vec{J} = -D\vec{\nabla}n$$

Fick's 1st Law

New USP <1207> states:

"Mathematical models appropriate to leak flow dynamics may be used to predict the time required for detectingleaks of various sizes or rates."

$$\frac{\partial \mathrm{P}_i(t)}{\partial t} = \frac{-D \cdot A_0}{V} \frac{\partial \mathrm{P}_i(z,t)}{\partial z}$$

$$\%Oxygen(t) = 20.9\% \cdot \left[1 - \mathbf{exp}\left(-\frac{\alpha_{Diff}}{V} t\right)\right]$$

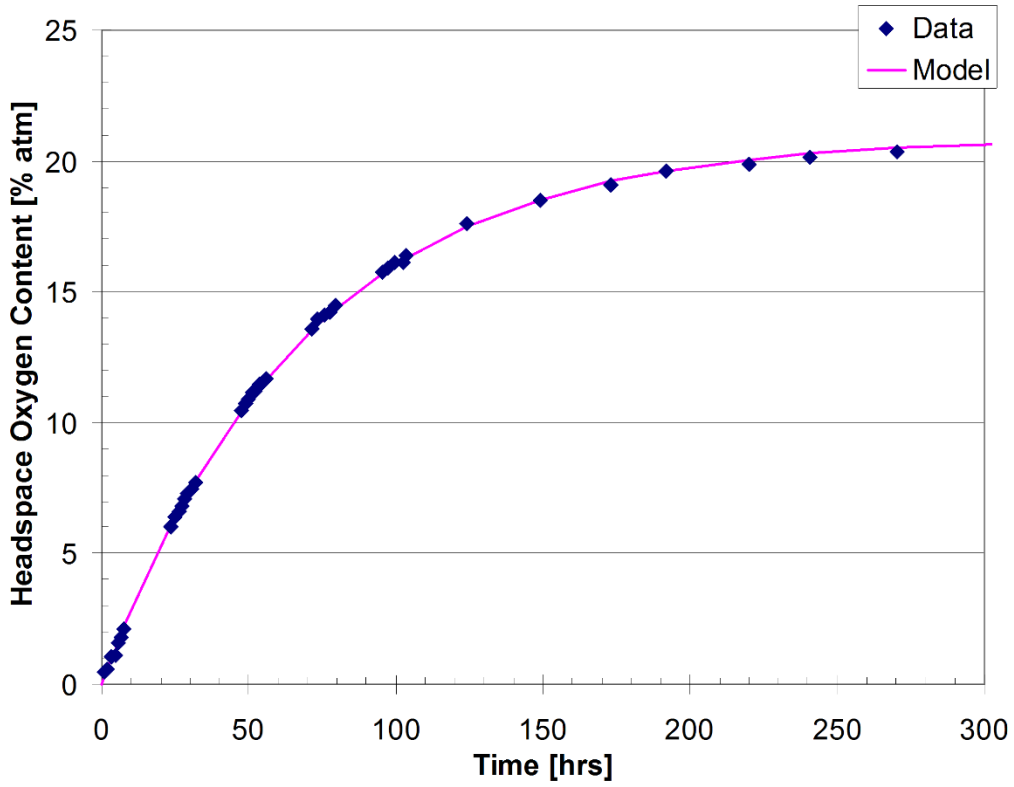
The change in oxygen concentration will be exponential with respect to time

Diffusion Parameter

$$\alpha_{Diff}\left[\frac{cm^3}{s}\right] = \frac{D \cdot A_0}{L}$$

The Diffusion Parameter is a function of the Diffusion Coefficient, *D*, the defect cross-sectional Area, A_0, and Depth, *L*.

Validation of Oxygen Ingress Model



With fixed values for:

D = 0.22 cm^2/s

A_0 = 20μm^2 (5µm ø)V = 18cc
(15R)

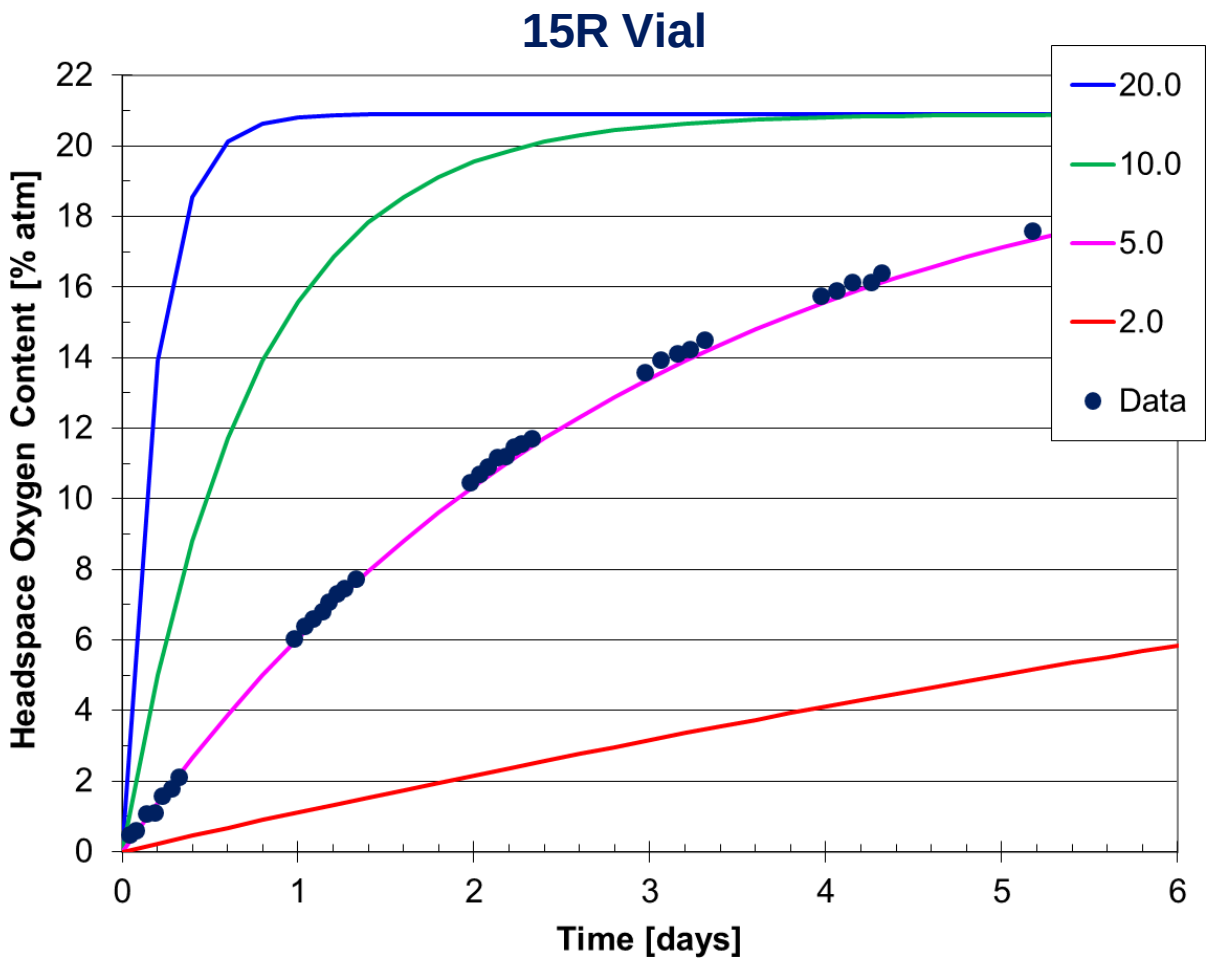
Obtain an empirical **depth parameter value:**

L = 6 µm

Oxygen Ingress Model Example

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

Defect diameter[· m



Part 3

INDUSTRY CASE STUDIESAND EXAMPLES

Overview of CCI case studies

1. Method development

2. Process optimization

3. Biologics Cold Storage CCI Study

4. 100% inspection of lyophilized product

Case study 1:
Method Development

Objective

- Detection of 5 micron leak within 30 minutes

Sample set

- 6R DIN clear tubing vial – 1.5mL product
- Positive controls: 2µm, 5µm,10µm and 15µm laser drilled defects
  - Glass defects
  - Metal plate defects

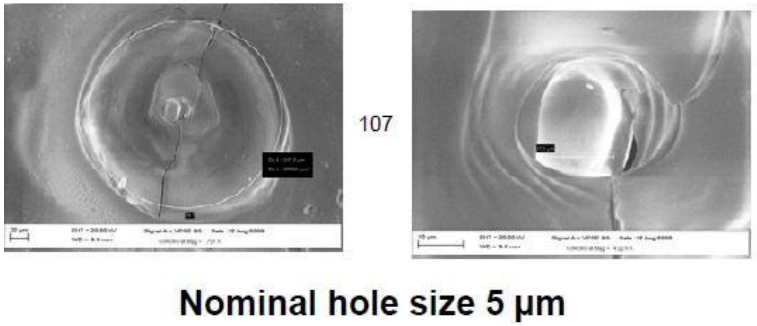
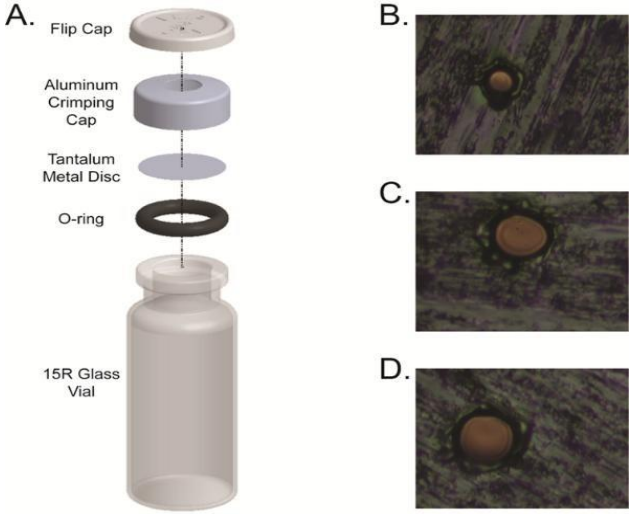


Image provided by Lenox Laser



Case study 1:
Method Development

- Phase 1: Manufacturing conditions

- Determine nitrogen purge conditions

- Phase 2: API reactivity

- Oxidation rate

- Phase 3: CCI Method development

- Diffusion test with vials with know defects (+ve controls)

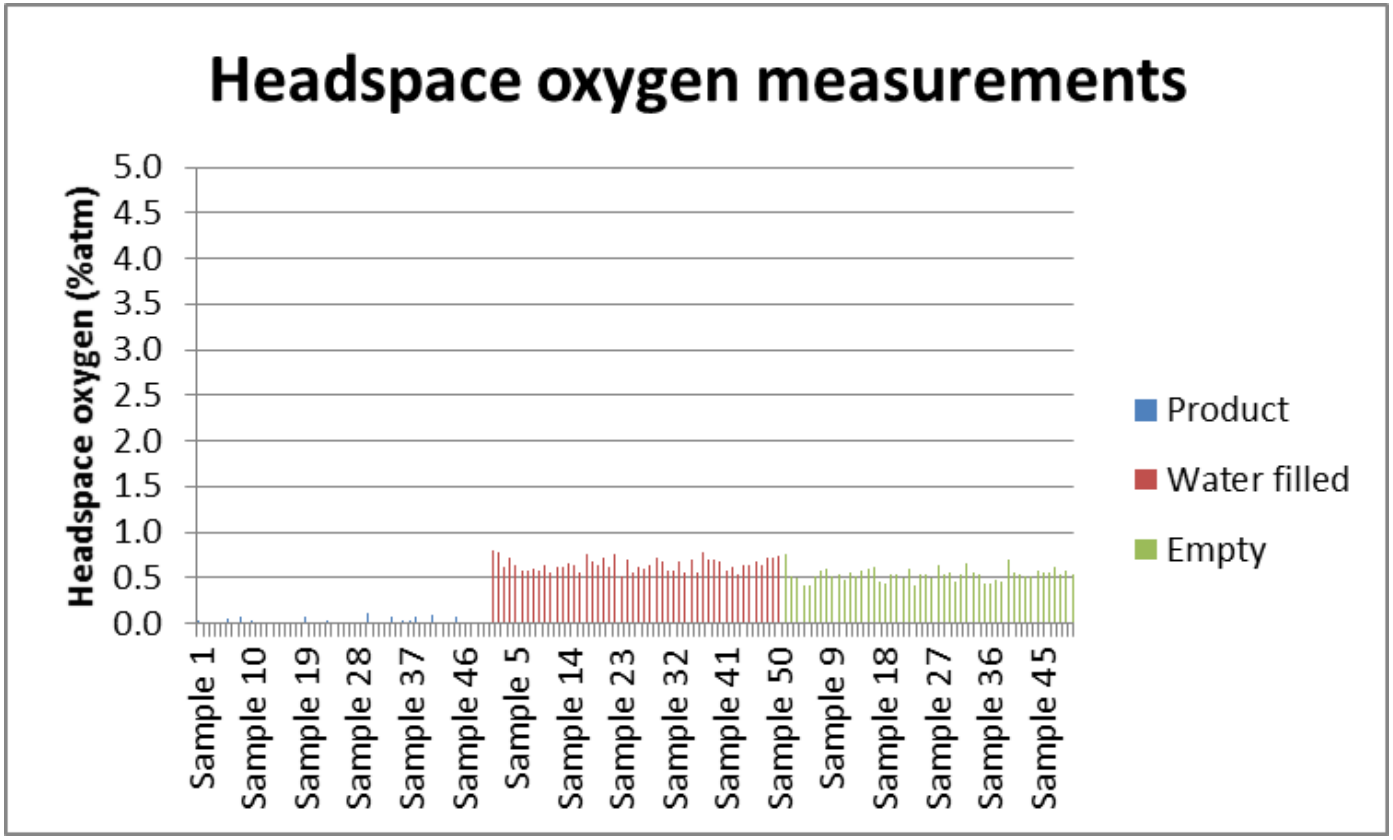
- Effusion test with vials with know defects (+ve controls)

- Method protocol

Case study 1:
Method Development

Phase 1: Manufacturing conditions

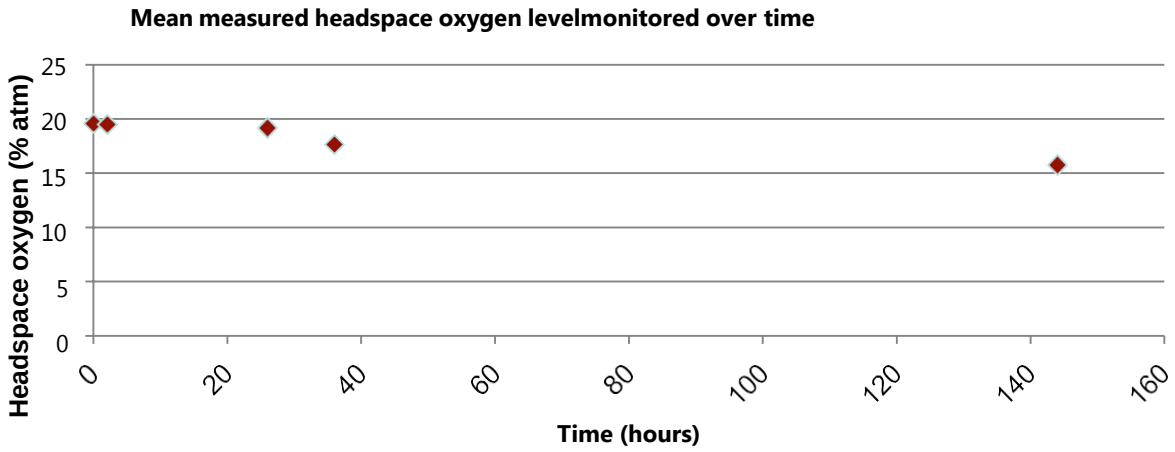
- 50 product, water-filled and empty samples



Case study 1:
Method Development

Phase 2: API reactivity

- 50 product samples opened to air and followed over time

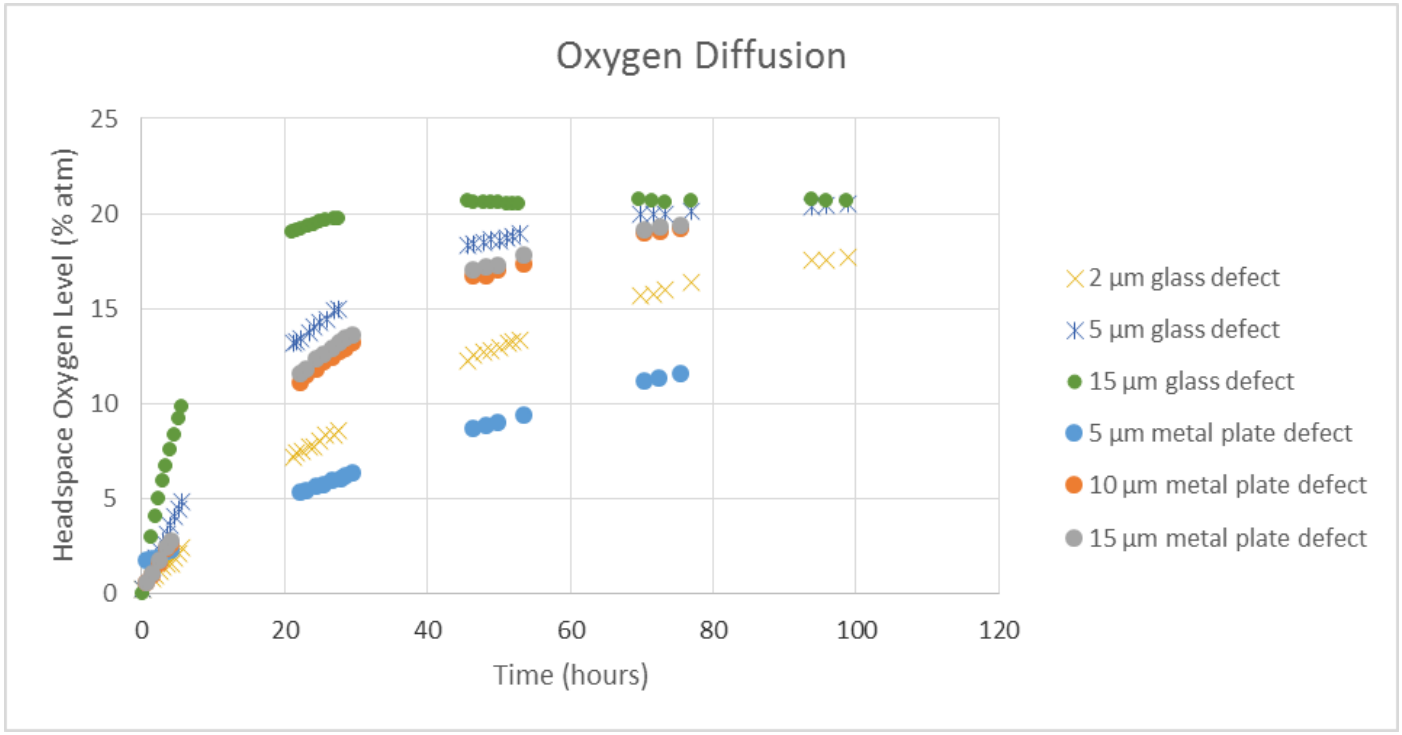


	Oxygen (% atm)
Start	19.59
2 hours	19.50
26 hours	19.18
36 hours	17.63
144 hours	15.76

Case study 1:
Method Development

Phase 3: CCI method development

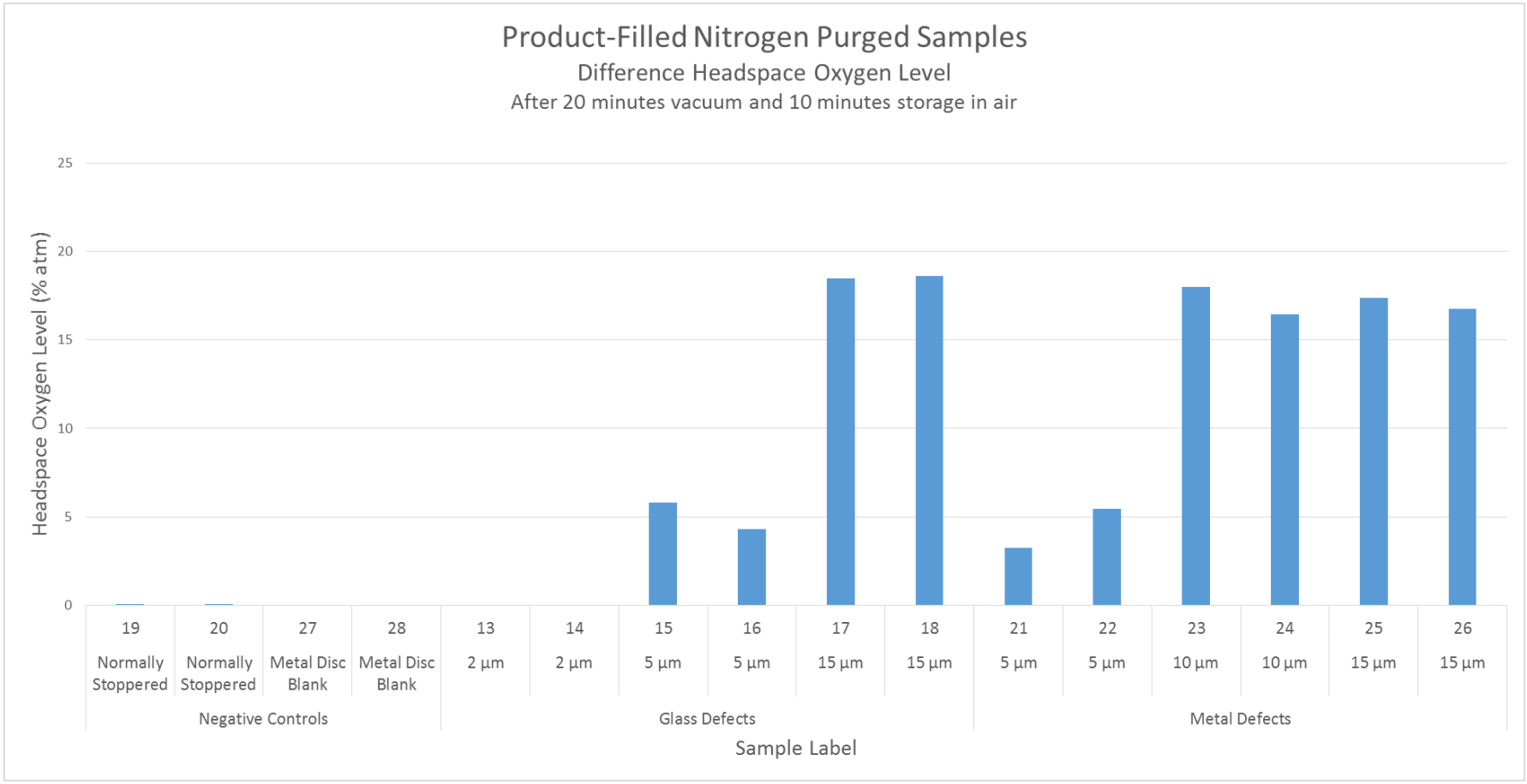
- Diffusion tests with vials with known defects



Case study 1:
Method Development

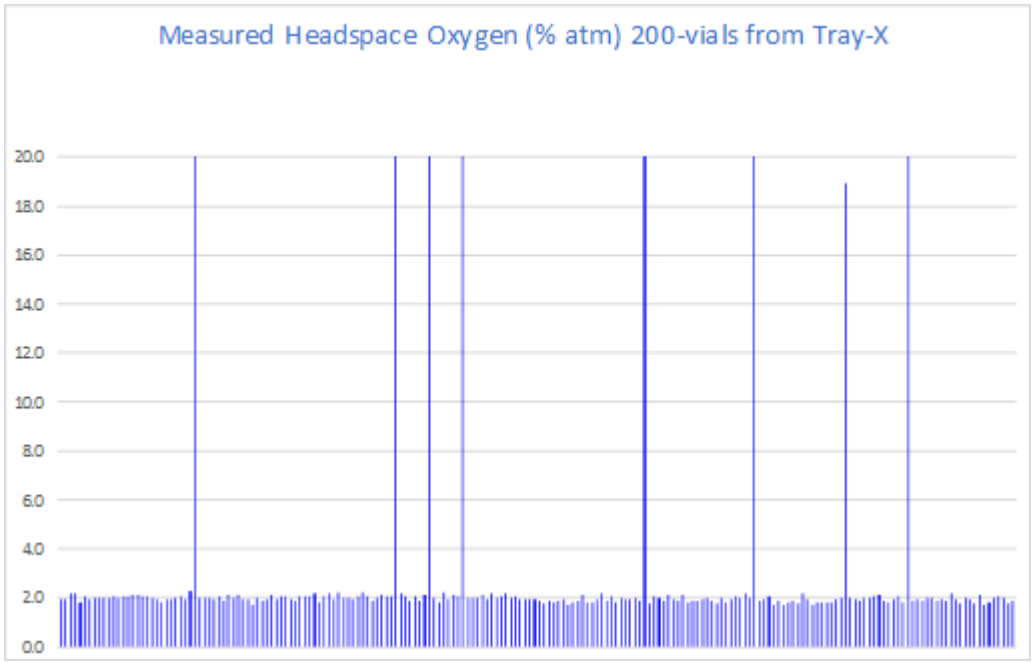
Phase 3: CCI method development

- Effusion tests with vials with known defects



Case study 26 :

Process optimisation



Case

- Liquid product in glass vial under N_2 atmosphere.
- All 200 vials passed visualinspection.

Result

- 192 accepted vials < 2% O_2
- 8 rejected vials ≈ 20% O_2
- Total test time for 200 vials: < 45 minutes

Case study 3:
CCI testing for vials stored on dry ice (CO_2)

- 2R vials containing a Biologic, headspace 1 atm of air
- Stored on dry ice for 7 days.
- Thawed to room temperature (RT).
- Headspace conditions analyzed.
  - Any change in the headspace condition would indicate a loss ofCCI during deep cold storage

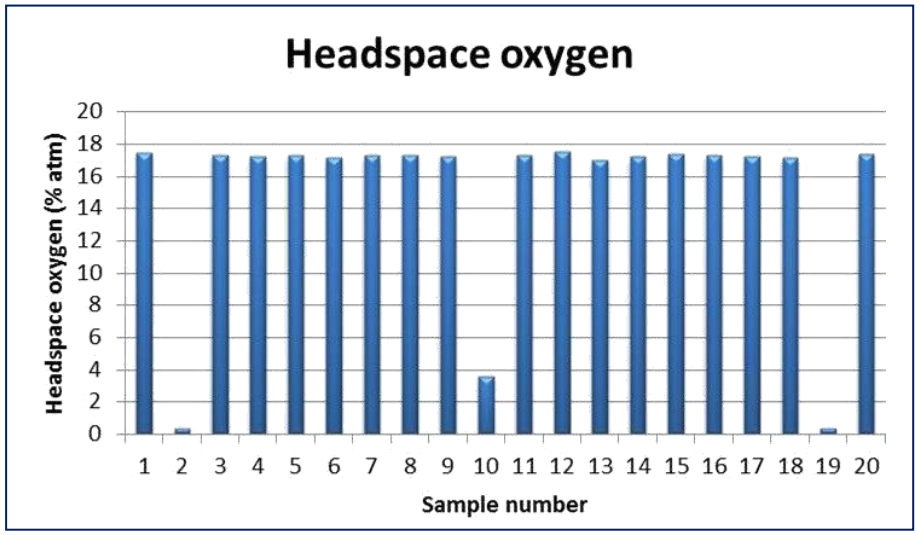
Case study 3:
CCI testing for vials stored on dry ice (CO2)

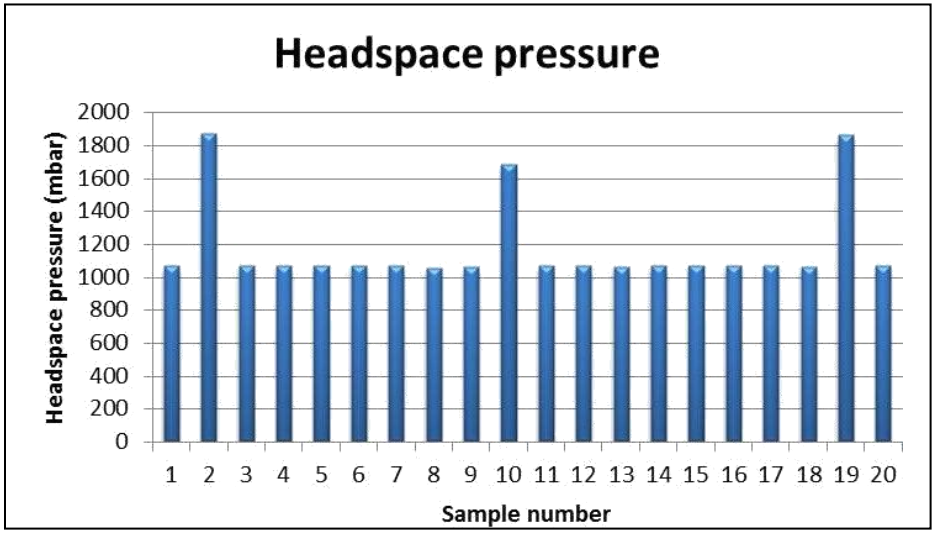
- Air headspace vial at 1atm at RT
- At low T, initial headspacecondenses and creates underpressure
- Stopper can lose elasticproperties & closure canbe lost
- Cold dense gas from storage environment fills headspace
- Warming container to RT,stopper regains elasticityand reseals trapping the cold dense gas in the vial

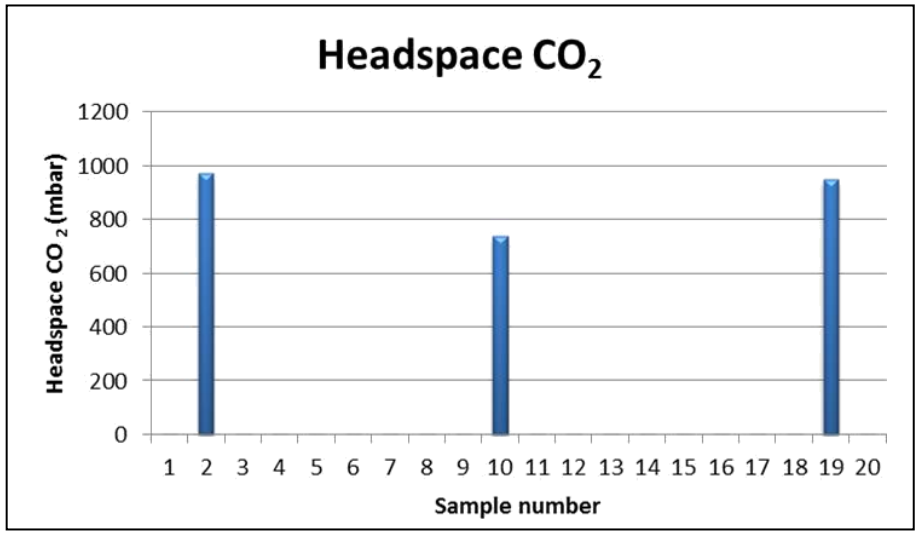
Case study 3:
CCI testing for vials stored on dry ice (CO2)

- The cold dense gas trapped inside, expands as temperature increases creating overpressure
- Headspace gas composition could alsochange depending on storage environment
- Maintenance of changed headspace conditions can be monitored over time toverify that the leak was temporary.

Case study 3:
CCI testing for vials stored on dry ice (CO2)







Three different headspace measurements identify the same 3vials as having CCI issues.

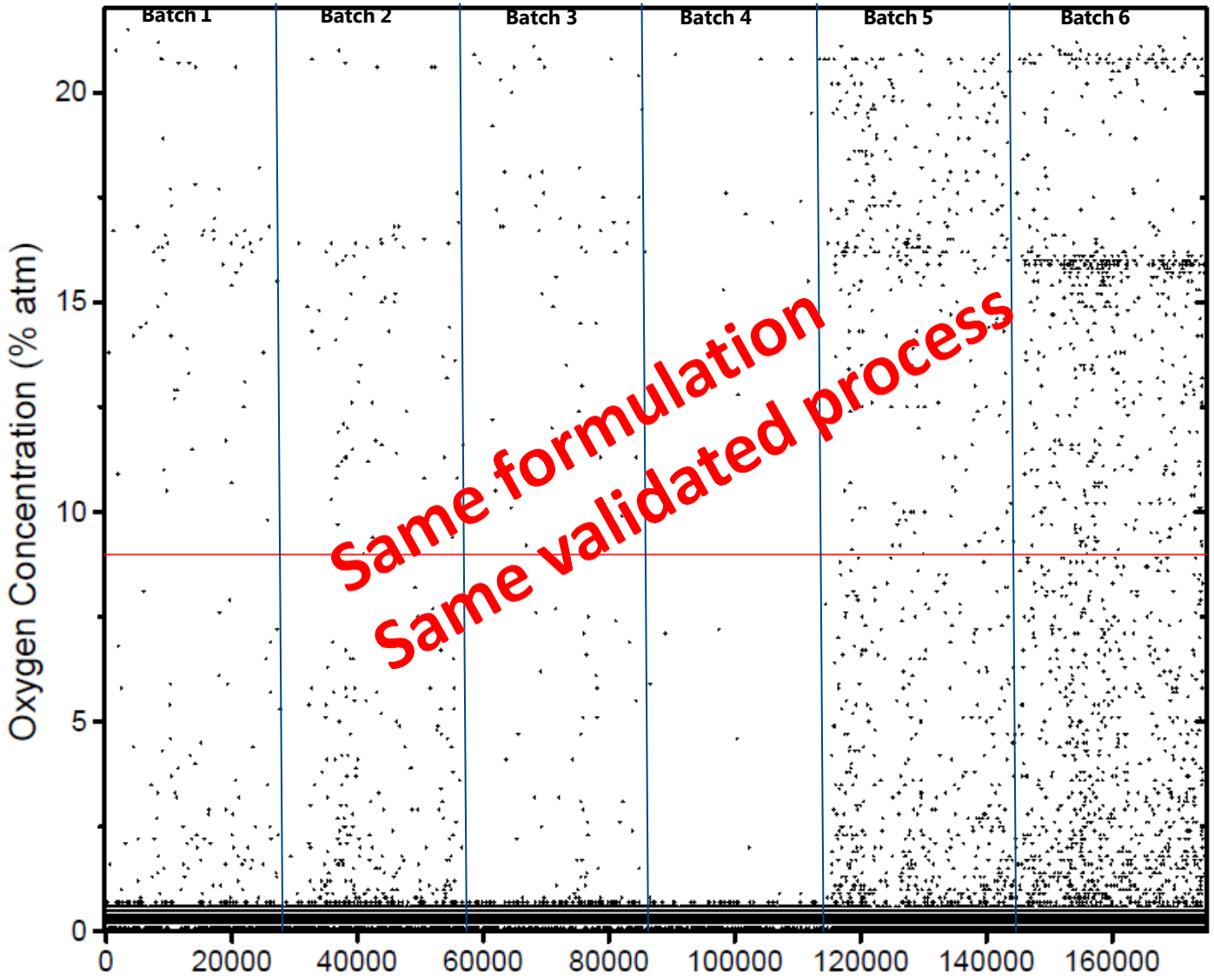
Case study 3:
CCI testing for vials stored on dry ice (CO_2)

Some important comments on these results:

- Leaks during deep cold storage are usually temporary!
- CCI methods requiring an active leak (blue dye, microbialingress, pressure/vacuum decay) will NOT identify these vials having temporary leaks.

Case study 4:

100% CCI testing of product

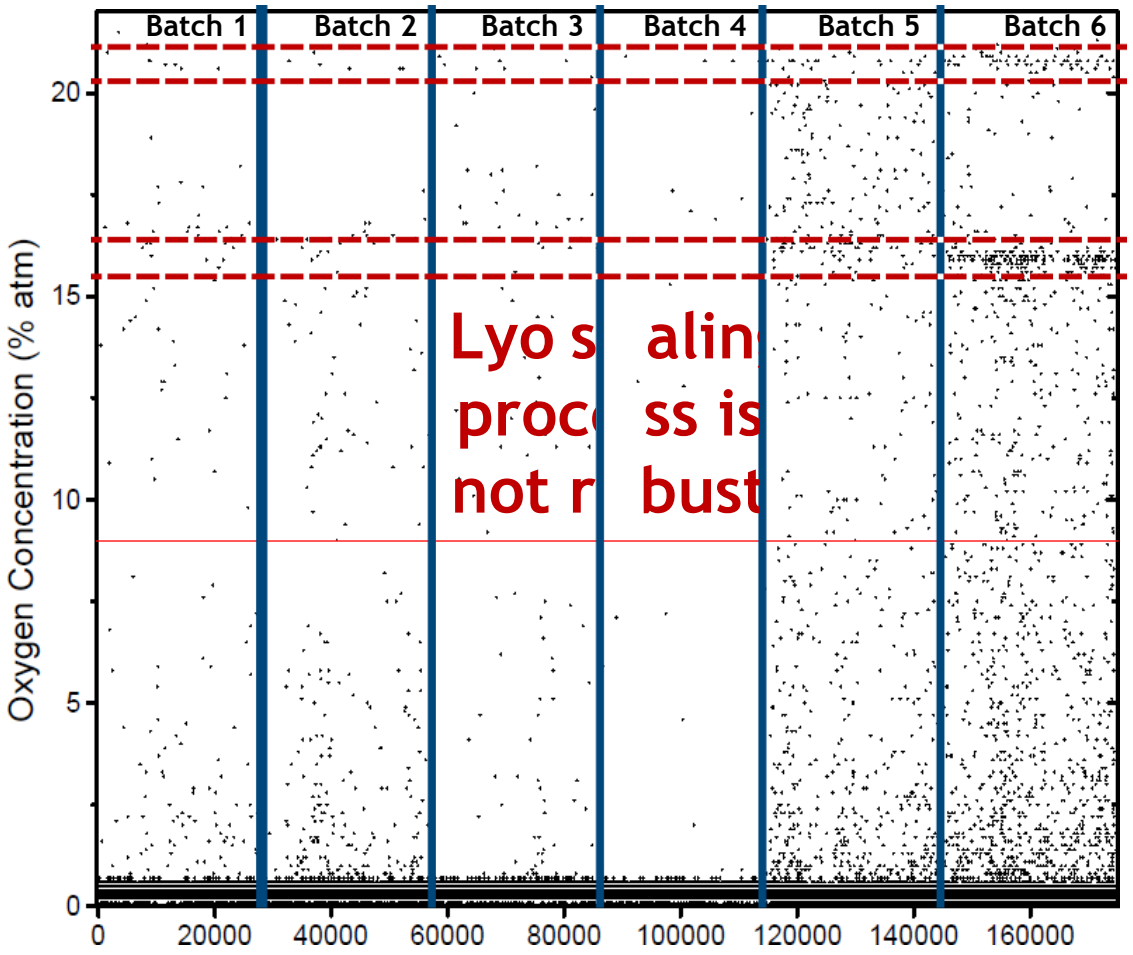


Lyophilised Product closedat 200 mbar of N_2

Results of 6 consecutive batches

Case study 4:

100% CCI testing of product



- 1 atm air vials, gross(permanent) leaks
- Lyo headspace specified to be 200 mbar N_2
- If 800 mbar air enters vial

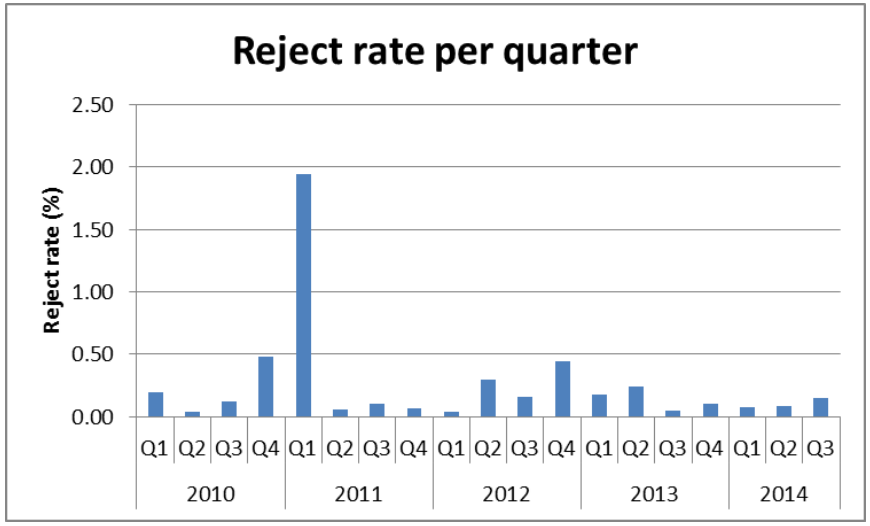
  = 16% O2!
- Partial leaks stopped bycapping

Case study 4:

100% CCI testing of product

Case 100% inspection

Results



5 years of manufacturing data:

- 156 lots
- Total 1.9 million vials

44-lots (28%) with zero rejectsAverage reject rate was 0.25%