Laser-based
Headspace Inspection

USP CHAPTER <1207>

PACKAGE INTEGRITY EVALUATION – STERILE PRODUCTS

Use of laser headspace analysis for deterministic evaluation of container closure integrity throughout the product lifecycle.

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VP Sales North America

Agenda

- USP <1207> Overview
- Laser-based headspace analysis for CCIT
- Leak detection and method validation
- Product Life-cycle Case Studies
  - Package Development
  - Process Development
  - In process monitoring in cGMP Manufacturing
  - Long-term Stability
- What can Lighthouse do to help?

Revised USP <1207>

Package Integrity Evaluation – Sterile Products

- Released to the public in February 2016
- Implementation scheduled for August 2016 when published as Supplement 39
- USP<1207> chapter includes 4 documents:
  - General Information **<1207>** Package Integrity Evaluation.
  - Package Integrity testing in the Product Life Cycle – Test Method Selection and Validation **<1207.1>**
  - Package Integrity Leak Test Technologies **<1207.2>**
  - Package Seal Quality Test Technologies **<1207.3>**

What has changed?

- Preference for **deterministic** CCI methods over old probabilistic methods
- Integrity definition = No leakage greater than the product-package **maximum allowable leak limit** (MALL)
- Recommends using CCI during the **entire** product life cycle
- **Eliminates** the requirement to compare new deterministic methods to old microbial immersion

USP <1207.1> Section 3.5

Deterministic	Probabilistic
Predictable chain of events	Series of sequential events and/or simultaneous events
Measured physical or chemical endpoint	Random outcome based on probability distribution
Objective & Quantitative results	Subjective & Qualitative results
Non-Destructive	Predominantly destructive
No sample preparation	Sample preparation required
Low risk of sample preparation error	High risk of sample preparation error

USP<1207.1 > Section 3.5 Deterministic or Probabilistic Methods

- **Deterministic Methods**:

  "…are capable of detecting leaks at clearly defined and predictable detection limits."

  "… are preferred when establishing the inherent integrity of a container closure system."

- **Probabilistic Methods**

  "…are best chosen when the method outcome requirements demand a specific probabilistic approach"

  "…are more challenging to design, develop, validate and implement."

USP <1207>

Table 1: Product Quality Risks posed by Leaks of Concern

Leaks of concern	Risk to Product Quality
Capable of allowing **entry of microorganism**	Failure of product sterility quality attribute
Capable of allowing **escape of the product** dosage form or allowing entry of external liquid or solid matter	Failure of relevant product physicochemical quality attributes
Capable of allowing **change in gas headspace** content. (i.e. loss of headspace inert gases, loss of headspace vacuum, and/or entry of gases)	Failure of relevant product physicochemical quality attributes and/or hindrance of product access by the end-user

Know your product and your product-package!

Determine product-package maximum allowable leak limit (MALL).

USP <1207.1> Section 3.9

Table 1: Gaseous Leak Rate versus Orifice Leak Size

	Detectable Leaks	
Row	**Air Leakage Rate* (scc/s)**	**Orifice Leak Size** (µm)**
1	$<1.4\ 10^{-6}$	<0.1
2	1.4×10^{-6} to 1.4×10^{-4}	0.1 to 1.0
3	$>1.4 \times 10^{-4}$ to 3.6×10^{-3}	>1.0 to 5.0
4	$>3.6 \times 10^{-3}$ to 1.4×10^{-2}	>5.0 to 10.0
5	$>1.4 \times 10^{-2}$ to 0.360	>10.0 to 50.0
6	>0.360	>50.0

* Dry Air leak rate at 1 atm differential pressure across an orifice leak at 25°C (i.e. vial at full vacuum)

** Nominal diameter orifice sizes assumes leak path of negligible length

USP <1207.2> Deterministic Leak Test Technologies

Leak test	Measurement Outcome	Leak Detection Range
Tracer-gas	**Helium Loss**	**<0.1 to 10 micron**
Laser-Headspace	**Gas Composition or Gas Pressure**	**<0.1 to > 50 micron**
HVLD	**Electrical Current**	**>1.0 to > 50 micron**
Pressure Decay	**Pressure Drop**	**>1.0 to > 50 micron**
Vacuum Decay	**Pressure Rise**	**>1.0 to > 50 micron**
Mass Extraction	**Mass Flow**	**>1.0 to > 50 micron**

While no single method is appropriate for all types of containers, laser headspace analysis is the only method that works for the full range of defects.

Maximum Allowable Leakage Limit (MALL)

- Section 3.4.1 Sterility

  "Tracer gas using vacuum mode and laser-based gas headspace analysis have both been shown to be sensitive enough to quantitatively analyze leakage through the smallest leak paths."

- Section 3.4.2 Sterility & Gas Headspace Content

  "Leak test options that include those that directly check for headspace pressure and/or content, such as laser-based headspace analysis"

- Section 4.2.4 Detection Limit

  "Laser-based headspace analysis may be able to identify the presence of leaks smaller that can be artificially created. The limit of detection can be mathematically predicted on the basis of gas flow kinetics."

USP <1207> Summary

- When USP<1207> is implemented in Aug-2016, regulators may begin to challenge new filings and annual addendums that use old probabilistic methods.

- Laser-based headspace methods are:
  - deterministic and therefore preferred.
  - appropriate for all Maximum Allowable Leak Limits (MALL).
  - used at all phases of the product life-cycle.

Laser-based
Headspace Inspection

LASER-BASED HEADSPACE ANALYSIS

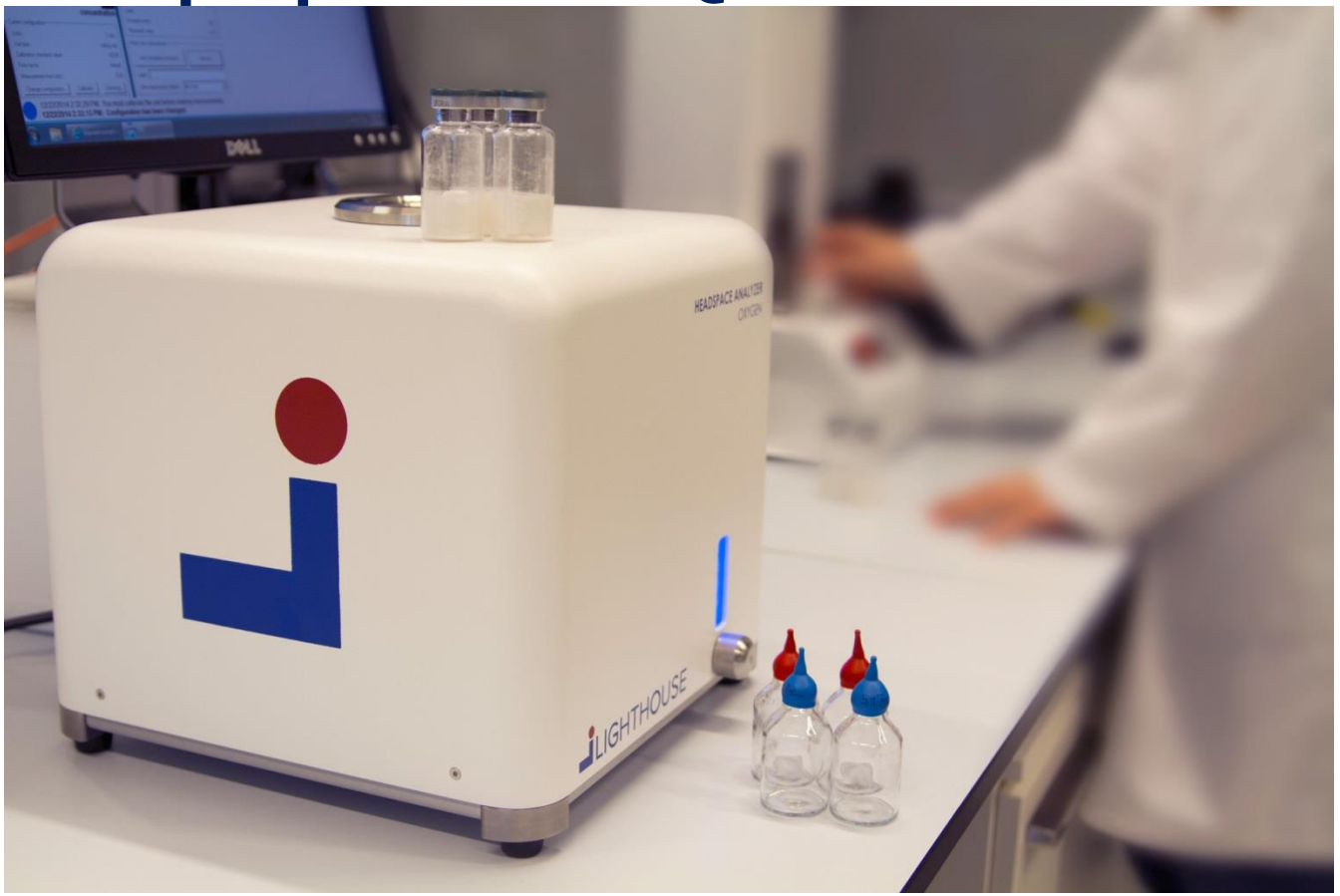
Headspace oxygen analysis

- The laser and photo-detector are optimized for measurement at 760nm, the unique wavelength that is specific for oxygen.
- Typical measurement only takes seconds to finish and provides quantitative insight into headspace conditions.
- Non-destructive nature allows time-evolved measurements for leak detection.

What type of product-packages?

- Sterile liquid, or lyophilized, or dry-powder filled
- Transparent rigid containers:
  - Clear or amber glass
  - Transparent plastics
- Vials, syringes, ampoules, cartridges
- Nominal volume ranging from 0.2mL to 250mL

Equipment Qualification



Headspace Analysis Laboratory Instrument

NIST Traceable Calibration Standards

Laser headspace analysis 3 of 5

Instrument Measurement Performance

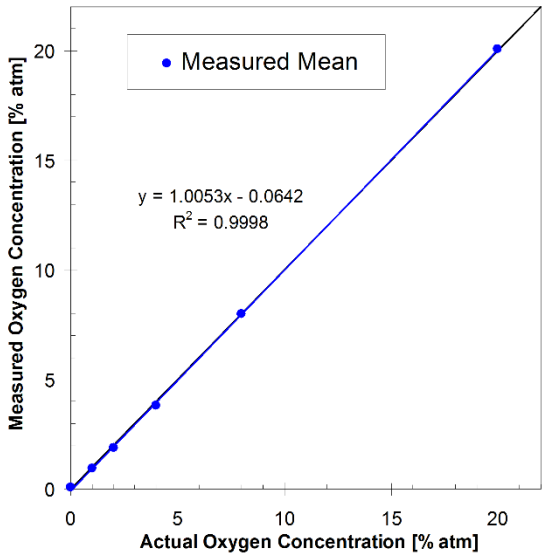
Assessing Instrument Accuracy, Precision, Linearity and Limit of Detection Using NIST Traceable Standards

N=10	Headspace Oxygen (% atm)			
Standard Label	Known Value	Meas. Mean	Error	St. Dev.
LH-3B-1A	0.00	0.1	0.1	0.07
LH-3B-1B	1.005	1.0	0.0	0.09
LH-3B-1C	2.002	1.9	-0.1	0.08
LH-3B-1D	3.998	3.8	-0.2	0.12
LH-3B-1E	8.002	8.0	0.0	0.10
LH-3B-1F	20.000	20.1	0.1	0.11

Time to complete less than 15-min

Accuracy

Precision



Linearity

Laser headspace analysis 4 of 5

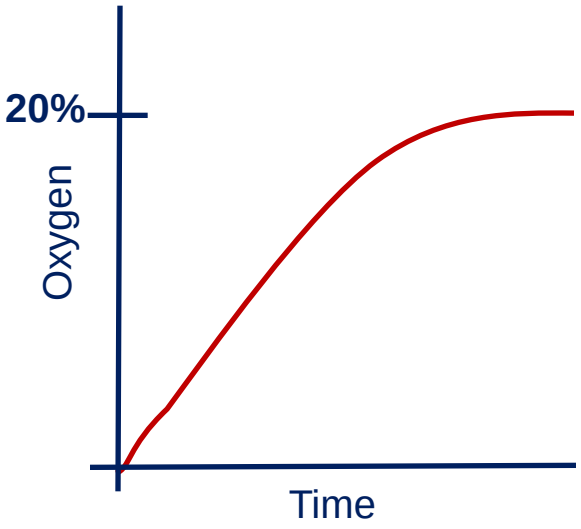
Lighthouse Validation Documentation

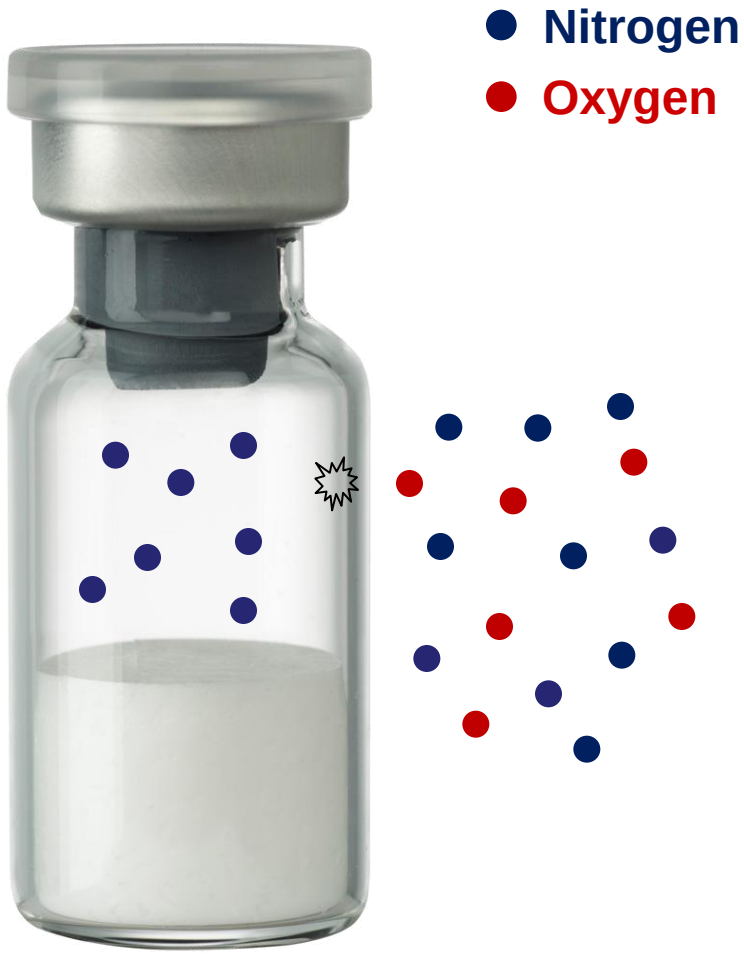
- Lighthouse offers a complete FMS system validation package including:
  - Functional Requirements (FR)
  - Design Specification (DS)
  - Traceability Matrix (TM)
  - Installation Qualification (IQ)
  - Operational Qualification (OQ)
  - 21-CFR-11 Compliance
- We can visit your site to install any upgrades and complete the validation of your system

How to detect leaks using Headspace Analysis?

- Measure changes in headspace gas composition or gas pressure
  - Headspace **oxygen** concentrations rising or falling indicate a leak.
  - Headspace **pressures** rising or falling indicate a leak.
  - Headspace **carbon dioxide** concentrations rising or falling indicate a leak.
- Measuring any change from the specified packaging conditions

How do sterile containers leak?
One way: oxygen diffusion into a vial





Oxygen Ingress Rate Model

- USP <1207> states:

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

- Molecular diffusion model derived from Fick's Law:

$$\%oxygen = 20.9\%\left(1 - \exp\left(-\alpha t\right)\right)$$

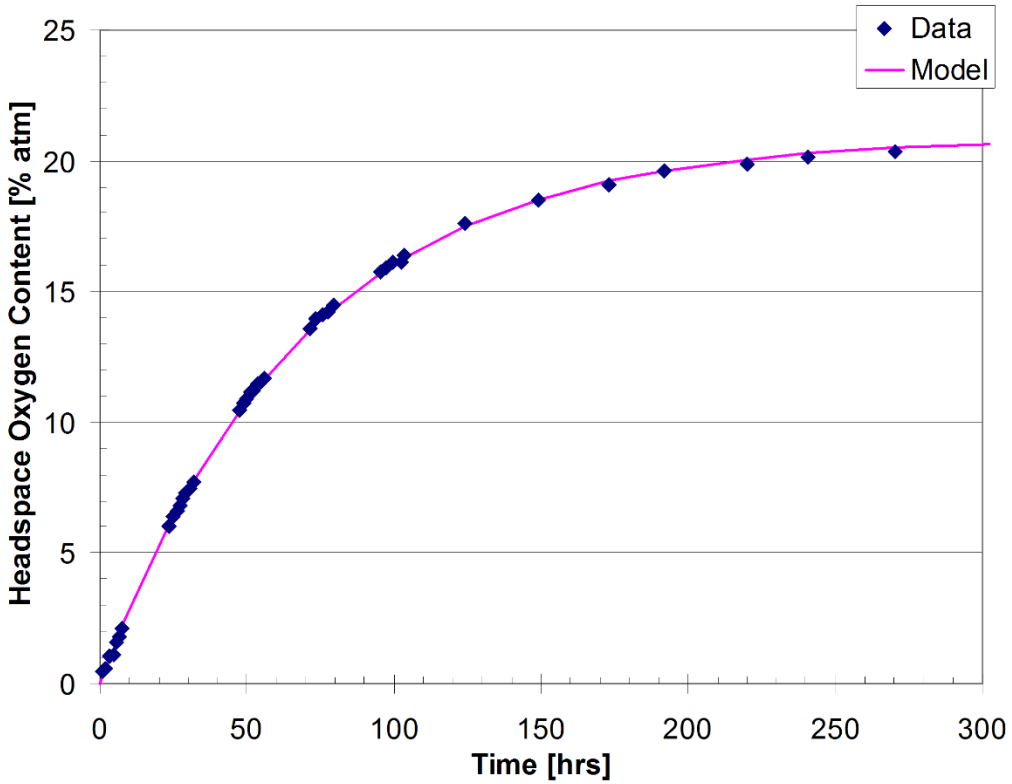
Oxygen ingress rate: $\alpha = \dfrac{D \cdot A_0}{z \cdot V}\left[s^{-1}\right]$

Oxygen Ingress Rate Model

- We can use this model 2-ways:
  - Knowing defect diameter and depth, we can use the model to predict the time required for oxygen ingress
  - Having actual oxygen versus time data for a real defect, we can calculate the ingress rate in scc/sec.

Validation of Oxygen Ingress Model

$$\%oxygen = 20.9\%\left(1 - \exp\left(-\alpha t\right)\right)$$



$$\alpha = \frac{D \cdot A_0}{z \cdot V}\left[s^{-1}\right]$$

With fixed values for:

$D = 0.22\ cm^2/s$

$A_0 = 20\mu m^2$ (5µm ø)

$V = 18cc$ (15R)

Obtain an empirical **depth parameter value:**

$z = 6\ \mu m$

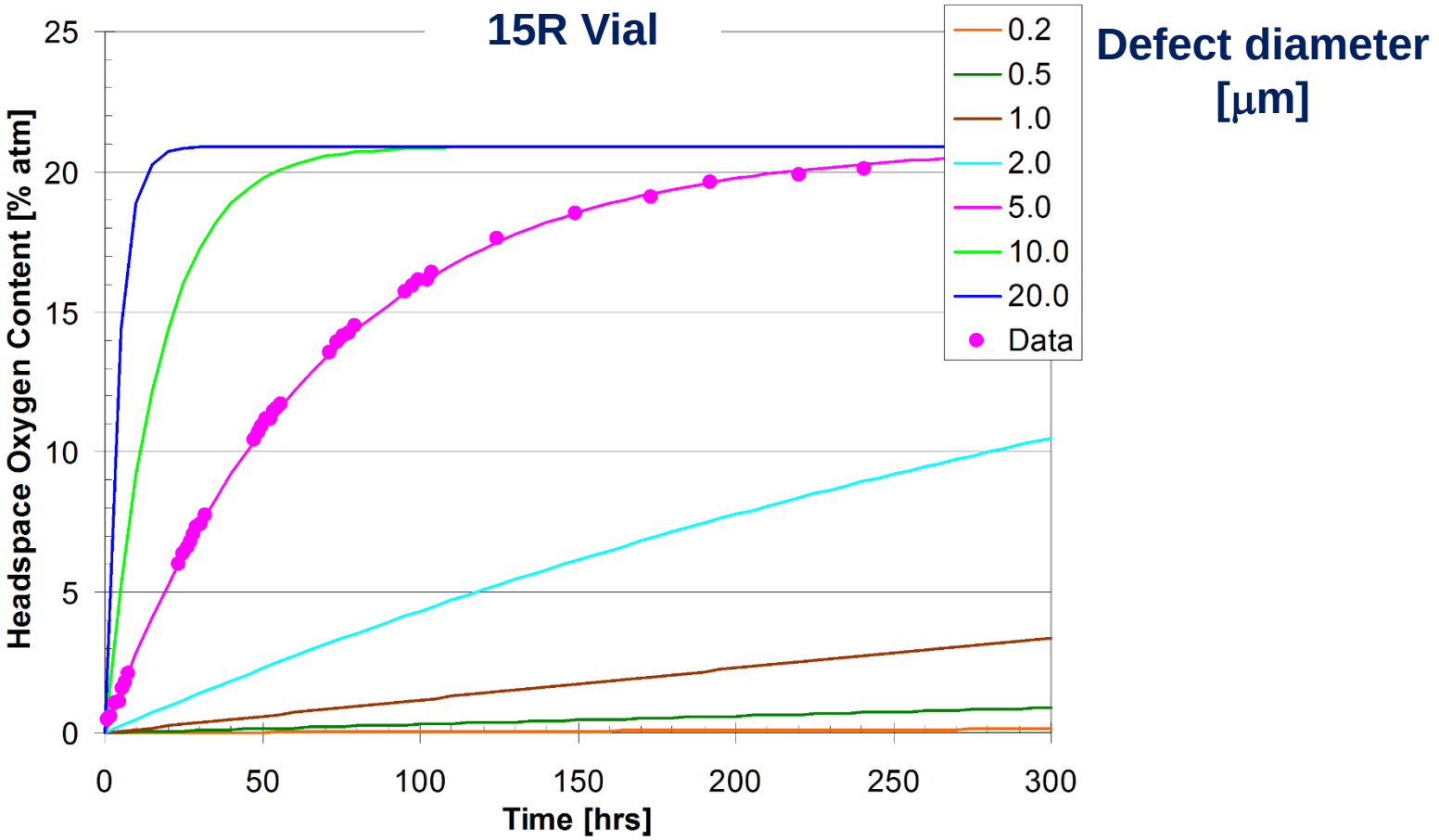
Model matches the data ±0.3 %-atm oxygen at every point

$\alpha = 7.6\times10^{-5}$ scc/sec oxygen ingress rate for this vial

Leak Detection 5 of 8

Oxygen Ingress Model Example

Leak rates for a range of defect sizes



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

Leak Detection 6 of 8

Time Required to Detect 4% Oxygen Ingress

15R Vial (18.8cc)	Detectable Leaks	
Time (hrs) to Reach 4%	Oxygen Ingress Rate* (scc/s)	Orifice Ingress Size** (µm)
9117	1.2×10^{-7}	0.2
1459	7.6×10^{-7}	0.5
365	3.1×10^{-6}	1.0
91	1.2×10^{-5}	2.0
15	7.6×10^{-5}	5.0
3.7	3.1×10^{-4}	10.0
0.9	1.2×10^{-3}	20.0

* Oxygen ingress during diffusive flow with only O_2 concentration difference

** Effective orifice size based on known ideal diameter and depth

Leak Detection Limits

- Lighthouse diffusive flow model accurately predicts oxygen/gas ingress time into container.
- The model predicts hold time for both positive and negative control vials during method development phase.
- Time evolved measurements will set realistic LOD
- Method development is completed when you have demonstrated ability to reliably detect leaks at or above the Maximum Allowable Leak Limit (MALL)

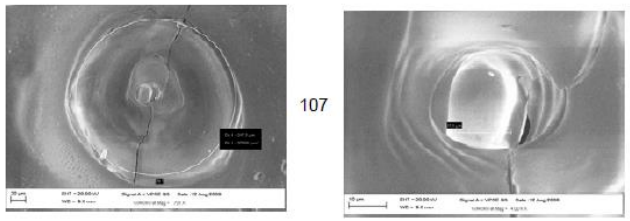
Method Validation

Protocol

- Use random mix of positive and negative control samples
- Test multiple days by multiple operators.

Sample set

- 15R DIN clear tubing vial (18.8mL)
- Positive controls: 2µm, 5µm and 10µm laser drilled defects & needle in stopper
- Positive control vials are nitrogen purged, sealed, and left in air.
- Negative controls: Flame sealed glass vials with 0% oxygen



Nominal hole size 5 µm

Image provided by Lenox Laser

USP <1207.1>

Section 4.3 System Suitability Validation

Defect Size	Test 1	Test 2	Test 3	Result
Negative Control	No leaks	No leaks	No leaks	No False Positives
2µm	100% detected	100% detected	100% detected	No False Negatives
5µm	100% detected	100% detected	100% detected	No False Negatives
10µm	100% detected	100% detected	100% detected	No False Negatives
100µm (needle)	100% detected	100% detected	100% detected	No False Negatives

Lighthouse USP<1207> Method Validation Protocol

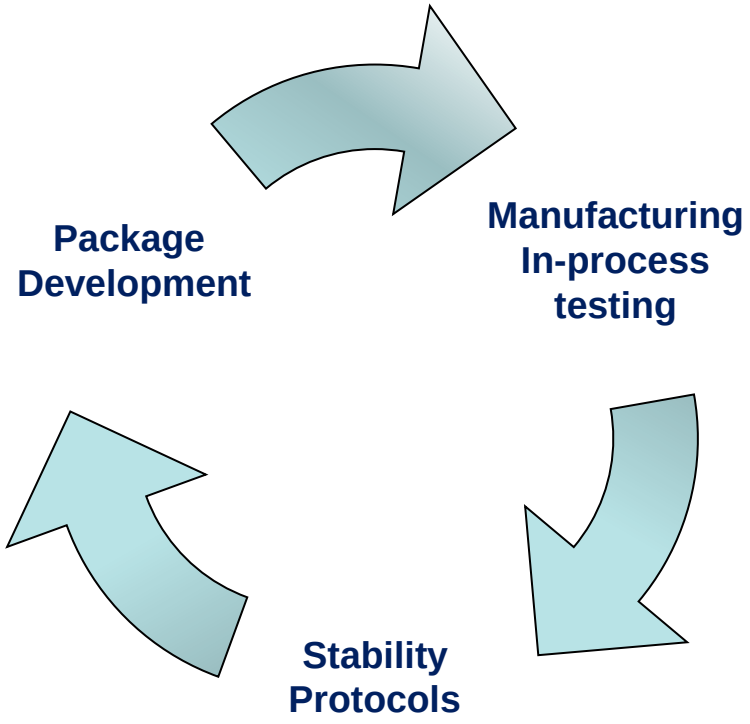
- Lighthouse can prepare a complete USP<1207> Method Validation Protocol for your container.
  - We offer on-site support to perform the 1st test session and train your team.
  - Your group will complete the 2nd and 3rd tests and issue the final report.

USP <1207> Full Life Cycle

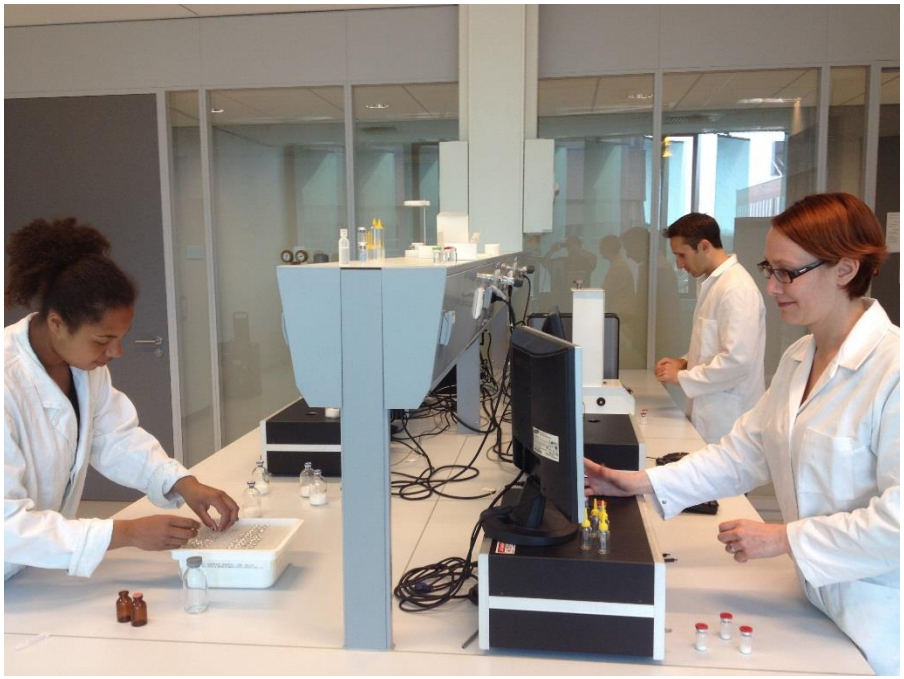
- USP <1207.2> states that:

  "Laser-based gas analysis may be used during any phase of the product life cycle."

- This includes package development, process development, routine manufacturing, and product stability testing.



Case Studies



Lighthouse Applications Labs in Charlottesville Virginia and Amsterdam Netherlands

60 Lab Projects in 2015 including:

- **CCI feasibility**
- **O_2 and H_20 stability**
- **-80C storage & shipment**
- **Permeation**

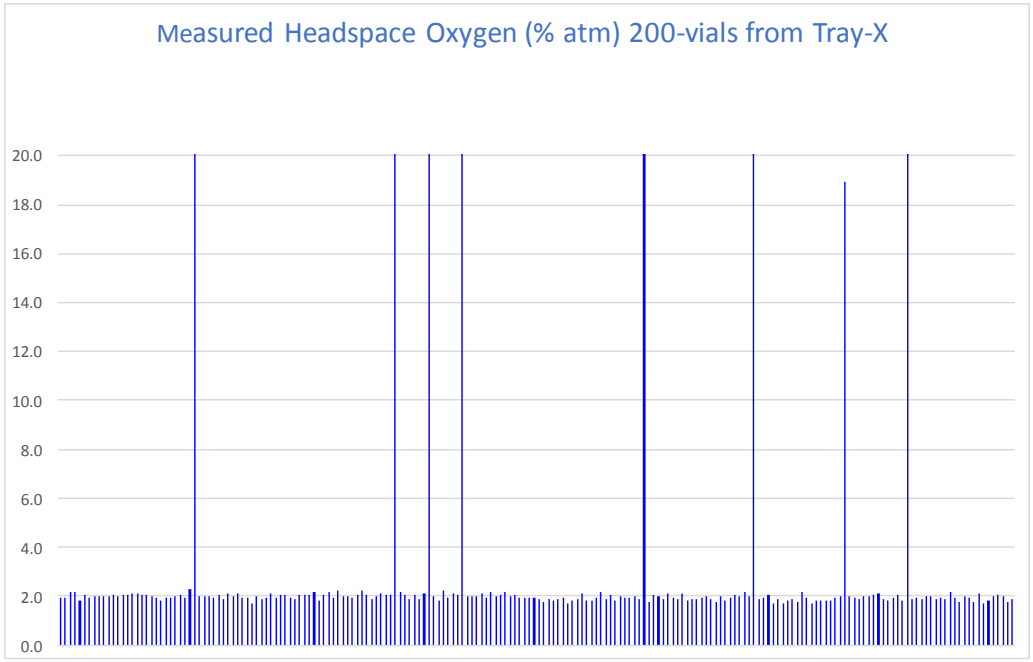
Process Development and Manufacturing

Confirm CCI for actual process conditions

Gather statistical information over multiple batches to assess risk

Implement 100% automated inspection where appropriate

Tech Transfer and Process Optimization



Case

CAPA found a process upset that created defective crimping

Defective vials had permanent leaks

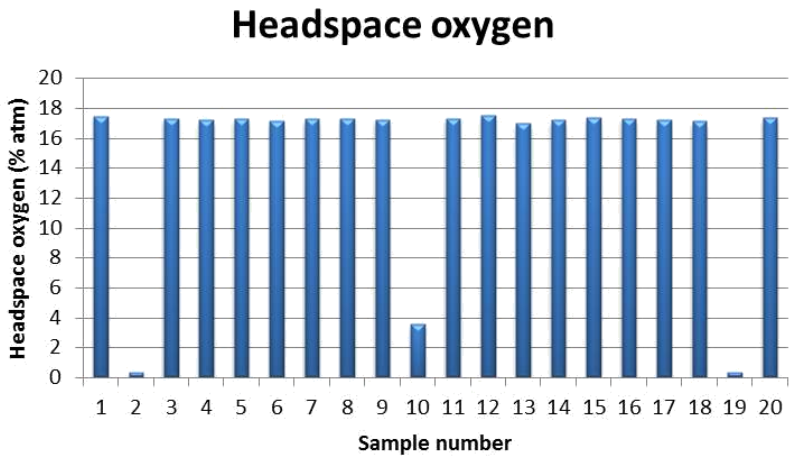
Result

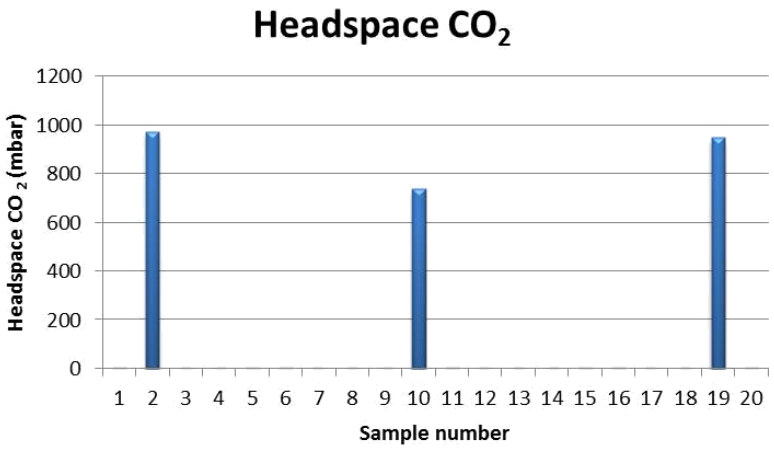
192 accepted vials < 2% O_2

8 rejected vials ≈ 20% O_2

Total time to test 200-vials was less than 45-min

Container closure integrity testing for vials stored on dry ice (CO_2)





Storage at -80°C increases risk of container closure integrity loss:

- Conventional rubber stoppers have a Tg ≈ -56°C.
- Stoppers lose elasticity at -80°C risking CO_2 ingress.

Lighthouse has helped multiple clients with packaging studies to find a solution.

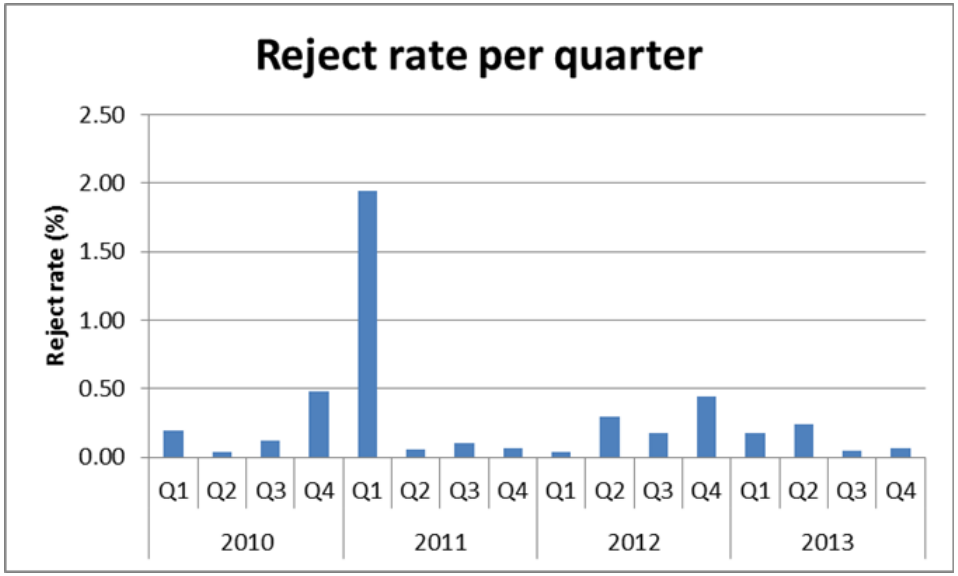
On-site Measurement Leases

FMS Headspace Analyzer Leases for Process optimization
- **12 on-site lease clients**
- **Duration:1 month to 3-months**

Lighthouse VISTA 100% automated Headspace inspection system

- **2 emergency inspections**
- **1 process characterization**

100% Inspection 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%

Difficult to manufacture a perfect batch

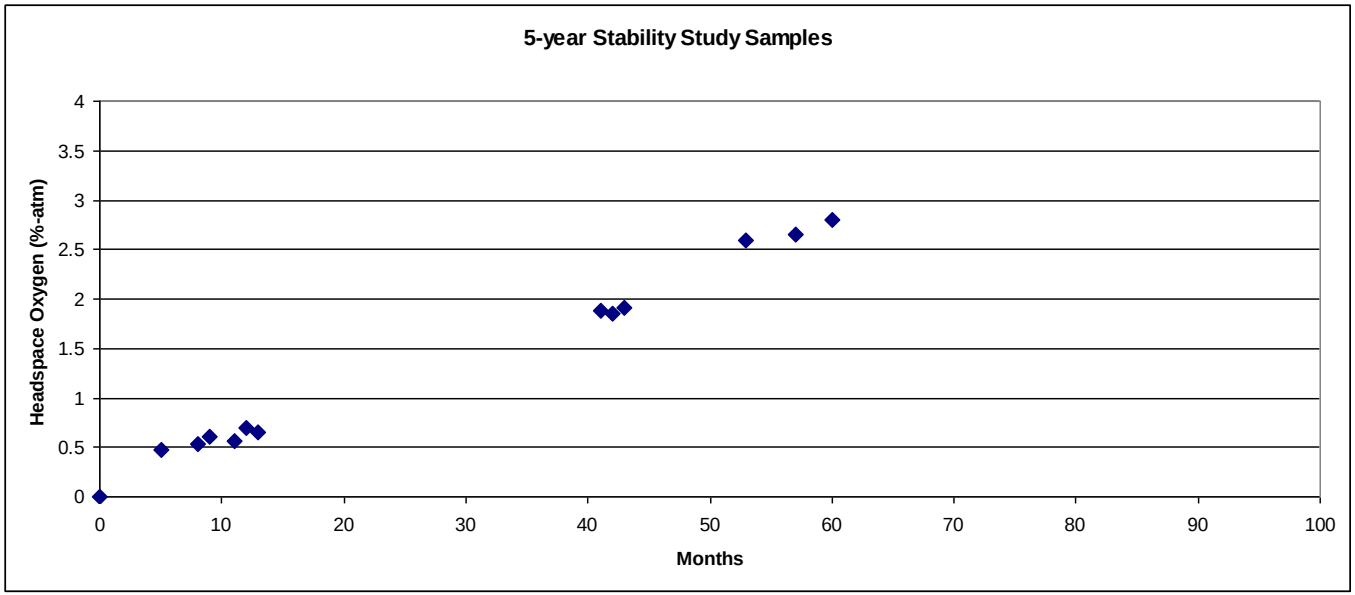
USA FDA Guidance to Industry

- "Container and Closure System Integrity testing *in lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products"
- Published by FDA in February 2008
- Now referenced in USP<1207>

CCI in lieu of sterility in stability protocols

- Fewer samples required in stability protocol
  - Sterility required at beginning and end only
- Detect defects before microbial ingress
- Eliminate incubation and reduce testing time
- Fewer false positives and false negatives

Long-term Oxygen Permeation



Using 12-samples from a long term stability study, the oxygen permeation rate was calculated at $8.79 \cdot 10^{-10}$.

Based on this rate, the product would reach 4% oxygen within 93 months

How can Lighthouse help?

- Lighthouse Application Lab Projects including:
  - Feasibility studies on *your* specific product-package system
  - Method Development studies using positive and negative control samples
- Method Validation Protocols designed for your product-package system to be performed at *your* site.
- Headspace analyzers for your team:
  - Short-term lease
  - Purchase

Summary

- If your team has been using dye-ingress methods, you will begin to have push-back from US FDA when submitting new applications, or annual amendments with new containers.

- We have assisted multiple pharmaceutical firms develop and validate laser-based headspace analysis to meet the new USP<1207> requirements.

- Email me at mlally@lighthouseinstruments.com for more information

Upcoming Events

- See Lighthouse Instruments at the following conferences:
  - PDA Annual Meeting
    - March 14-16 in San Antonio, TX
  - Interphex
    - April 26-28 in NYC, NY