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

<table>
<thead>
<tr>
<th>Deterministic</th>
<th>Probabilistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictable chain of events</td>
<td>Series of sequential events and/or simultaneous events</td>
</tr>
<tr>
<td>Measured physical or chemical endpoint</td>
<td>Random outcome based on probability distribution</td>
</tr>
<tr>
<td>Objective &amp; Quantitative results</td>
<td>Subjective &amp; Qualitative results</td>
</tr>
<tr>
<td>Non-Destructive</td>
<td>Predominantly destructive</td>
</tr>
<tr>
<td>No sample preparation</td>
<td>Sample preparation required</td>
</tr>
<tr>
<td>Low risk of sample preparation error</td>
<td>High risk of sample preparation error</td>
</tr>
</tbody>
</table>
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.”
Table 1: Product Quality Risks posed by Leaks of Concern

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

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

<table>
<thead>
<tr>
<th>Row</th>
<th>Air Leakage Rate* (scc/s)</th>
<th>Orifice Leak Size** (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;1.4 x 10⁻⁶</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>2</td>
<td>1.4 x 10⁻⁶ to 1.4 x 10⁻⁴</td>
<td>0.1 to 1.0</td>
</tr>
<tr>
<td>3</td>
<td>&gt;1.4 x 10⁻⁴ to 3.6 x 10⁻³</td>
<td>&gt;1.0 to 5.0</td>
</tr>
<tr>
<td>4</td>
<td>&gt;3.6 x 10⁻³ to 1.4 x 10⁻²</td>
<td>&gt;5.0 to 10.0</td>
</tr>
<tr>
<td>5</td>
<td>&gt;1.4 x 10⁻² to 0.360</td>
<td>&gt;10.0 to 50.0</td>
</tr>
<tr>
<td>6</td>
<td>&gt;0.360</td>
<td>&gt;50.0</td>
</tr>
</tbody>
</table>

* 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**

<table>
<thead>
<tr>
<th>Leak test</th>
<th>Measurement Outcome</th>
<th>Leak Detection Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracer-gas</td>
<td>Helium Loss</td>
<td>&lt;0.1 to 10 micron</td>
</tr>
<tr>
<td>Laser-Headspace</td>
<td>Gas Composition or Gas Pressure</td>
<td>&lt;0.1 to &gt; 50 micron</td>
</tr>
<tr>
<td>HVLD</td>
<td>Electrical Current</td>
<td>&gt;1.0 to &gt; 50 micron</td>
</tr>
<tr>
<td>Pressure Decay</td>
<td>Pressure Drop</td>
<td>&gt;1.0 to &gt; 50 micron</td>
</tr>
<tr>
<td>Vacuum Decay</td>
<td>Pressure Rise</td>
<td>&gt;1.0 to &gt; 50 micron</td>
</tr>
<tr>
<td>Mass Extraction</td>
<td>Mass Flow</td>
<td>&gt;1.0 to &gt; 50 micron</td>
</tr>
</tbody>
</table>

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 ANALYSIS
Headspace oxygen analysis

Laser light matches absorption frequency of target molecule.

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

- 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

<table>
<thead>
<tr>
<th>N=10</th>
<th>Headspace Oxygen (% atm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard Label</td>
</tr>
<tr>
<td></td>
<td>LH-3B-1A</td>
</tr>
<tr>
<td></td>
<td>LH-3B-1B</td>
</tr>
<tr>
<td></td>
<td>LH-3B-1C</td>
</tr>
<tr>
<td></td>
<td>LH-3B-1D</td>
</tr>
<tr>
<td></td>
<td>LH-3B-1E</td>
</tr>
<tr>
<td></td>
<td>LH-3B-1F</td>
</tr>
</tbody>
</table>

- **Accuracy**: Laser headspace analysis 4 of 5
- **Precision**: Time to complete less than 15-min
- **Linearity**: $y = 1.005x - 0.0642$, $R^2 = 0.9996$
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 concentration over time.

Nitrogen
Oxygen

Leak Detection 2 of 8
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:

\[
\%_{\text{oxygen}} = 20.9\% \left( 1 - \exp\left( -\alpha t \right) \right)
\]

Oxygen ingress rate: \( \alpha = \frac{D \cdot A_0}{z \cdot V} \) [s\(^{-1}\)]
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

\[ \% \text{oxygen} = 20.9\% \left(1 - \exp\left(-\alpha t\right)\right) \]

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

With fixed values for:
- \( D = 0.22 \text{ cm}^2/\text{s} \)
- \( A_0 = 20 \mu\text{m}^2 \) (5 µm ø)
- \( V = 18 \text{cc} \) (15R)

Obtain an empirical depth parameter value:
\[ z = 6 \mu\text{m} \]

Model matches the data ±0.3 %-atm oxygen at every point
\[ \alpha = 7.6 \times 10^{-5} \text{ scc/sec} \] oxygen ingress rate for this vial
Oxygen Ingress Model Example

Leak rates for a range of defect sizes

*Predicted* oxygen concentration versus time for *ideal defects*
# Time Required to Detect 4% Oxygen Ingress

<table>
<thead>
<tr>
<th>15R Vial (18.8cc)</th>
<th>Detectable Leaks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (hrs) to Reach 4%</td>
<td>Oxygen Ingress Rate* (scc/s)</td>
</tr>
<tr>
<td>9117</td>
<td>$1.2 \times 10^{-7}$</td>
</tr>
<tr>
<td>1459</td>
<td>$7.6 \times 10^{-7}$</td>
</tr>
<tr>
<td>365</td>
<td>$3.1 \times 10^{-6}$</td>
</tr>
<tr>
<td>91</td>
<td>$1.2 \times 10^{-5}$</td>
</tr>
<tr>
<td>15</td>
<td>$7.6 \times 10^{-5}$</td>
</tr>
<tr>
<td>3.7</td>
<td>$3.1 \times 10^{-4}$</td>
</tr>
<tr>
<td>0.9</td>
<td>$1.2 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

* 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

Image provided by Lenox Laser

Nominal hole size 5 µm
### USP <1207.1>
Section 4.3 System Suitability Validation

<table>
<thead>
<tr>
<th>Defect Size</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Control</td>
<td>No leaks</td>
<td>No leaks</td>
<td>No leaks</td>
<td>No False Positives</td>
</tr>
<tr>
<td>2µm</td>
<td>100% detected</td>
<td>100% detected</td>
<td>100% detected</td>
<td>No False Negatives</td>
</tr>
<tr>
<td>5µm</td>
<td>100% detected</td>
<td>100% detected</td>
<td>100% detected</td>
<td>No False Negatives</td>
</tr>
<tr>
<td>10µm</td>
<td>100% detected</td>
<td>100% detected</td>
<td>100% detected</td>
<td>No False Negatives</td>
</tr>
<tr>
<td>100µm (needle)</td>
<td>100% detected</td>
<td>100% detected</td>
<td>100% detected</td>
<td>No False Negatives</td>
</tr>
</tbody>
</table>
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 1\textsuperscript{st} test session and train your team.
  - Your group will complete the 2\textsuperscript{nd} and 3\textsuperscript{rd} 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

60 Lab Projects in 2015 including:
• CCI feasibility
• O₂ and H₂O stability
• -80°C storage & shipment
• Permeation

Lighthouse Applications Labs in Charlottesville Virginia and Amsterdam Netherlands
Process Development and Manufacturing

1. Confirm CCI for actual process conditions
2. Gather statistical information over multiple batches to assess risk
3. 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% O₂
8 rejected vials ≈ 20% O₂

Total time to test 200-vials was less than 45-min
Storage at -80°C increases risk of container closure integrity loss:
- Conventional rubber stoppers have a $T_g \approx -56°C$.
- 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