Automated Deterministic Inspection Technologies:
Complete Quality Control for Vials and Syringes

Oliver Stauffer, CEO
PTI Inspection Systems
Pharma’s Future

- Antibody-Drug Conjugates (ADC’s)
- Advanced gene therapy (RNA)
- Personalized therapy (CAR-T)
- Target therapy (mAbs)

LARGE MOLECULE PARENTERAL DELIVERY
Shift in CCI

• USP Chapter 1207 (2019)– Package Integrity Evaluation – Sterile Products
• EMA Annex 1 (2020)– Manufacture of Sterile Medicinal Products
Smallest leak to allow ingress determination


- Glass micro-pipettes through wall of stoppered glass vial
- 0.1 to 10μm diameter (Sized via helium mass spec)
- Microbial challenge by immersion + liquid tracer element
- Challenge conditions
  - Water bath immersion 60ºC 2hr, then 25ºC 1hr
  - 24 hr immersion, ambient pressure

Ingress Risk Dropped: Log -3.8 sccs (Leak < ~1μm)

No Ingress: Log -5 to -5.8 sccs (Leak ~0.3 to 0.2μm)

Most bacteria are 0.2 μm in diameter and 2-8 μm in length. The three basic bacterial shapes are coccus (spherical), bacillus (rod-shaped), and spiral (twisted), however pleomorphic bacteria can assume several shapes.
• CCI and Component Performance
  ➢ Dimensional tolerances
  ➢ Stopper and tip-cap
  ➢ Barrel barrier properties
• Barrel – Plunger(piston)
• Needle Shield - Needle Tip & Barrel
• Plunger Ribs
• Headspace Criticality
# Dye Ingress Test Methods

<table>
<thead>
<tr>
<th>Test Method</th>
<th>Ph.Eur. 3.2.9 USP 31 &lt;381&gt;</th>
<th>Modified USP/PhEur</th>
<th>ISO 8362-5 ISO</th>
<th>Modified ISO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dye Solution</td>
<td>1 g/L (0.1% w/v) Methylene Blue Aqueous Solution</td>
<td>1 g/L (0.1% w/v) Methylene Blue Aqueous Solution</td>
<td>0.1% w/v Methylene Blue Aqueous Solution</td>
<td>0.1% w/v Methylene Blue Aqueous Solution</td>
</tr>
<tr>
<td>Vacuum</td>
<td>-27 kPa</td>
<td>-37 kPa</td>
<td>75 ± 5 kPa¹</td>
<td>63 kPa²</td>
</tr>
<tr>
<td>Time Vacuum</td>
<td>10 minutes</td>
<td>10 minutes</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Time</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Atmospheric Pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ equivalent to drawing a vacuum of about -25 kPa
² equivalent to drawing a vacuum of about -37 kPa
<table>
<thead>
<tr>
<th>Defect Type</th>
<th>ID Code 1</th>
<th>Leak Test Results</th>
<th>Visual Inspection Results 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dP Pa</td>
<td>P/F</td>
<td>Inspector 4</td>
</tr>
<tr>
<td>Controls Tested for Ingress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B6</td>
<td>8</td>
<td>P</td>
<td>N</td>
</tr>
<tr>
<td>B7</td>
<td>8</td>
<td>P</td>
<td>N</td>
</tr>
<tr>
<td>B8</td>
<td>8</td>
<td>P</td>
<td>N</td>
</tr>
<tr>
<td>B9</td>
<td>8</td>
<td>P</td>
<td>N</td>
</tr>
<tr>
<td>B10</td>
<td>8</td>
<td>P</td>
<td>N</td>
</tr>
<tr>
<td>5µm hole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>111</td>
<td>64</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>112</td>
<td>54</td>
<td>F</td>
<td>N</td>
</tr>
<tr>
<td>113</td>
<td>88</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>114</td>
<td>56</td>
<td>F</td>
<td>N</td>
</tr>
<tr>
<td>115</td>
<td>46</td>
<td>F</td>
<td>N</td>
</tr>
<tr>
<td>10µm hole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>192</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>127</td>
<td>184</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>128</td>
<td>186</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>129</td>
<td>301</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>130</td>
<td>194</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>15µm hole</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>141</td>
<td>352</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>142</td>
<td>356</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>143</td>
<td>346</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>144</td>
<td>445</td>
<td>F</td>
<td>Y</td>
</tr>
<tr>
<td>145</td>
<td>371</td>
<td>F</td>
<td>Y</td>
</tr>
</tbody>
</table>

1 Holed syringes are identical to those used for Part 1, ASTM precision and bias studies.
2 Y = dye seen, N = No dye seen
Vacuum Decay Container/Closure Integrity Testing Technology. Part 2. Comparison to Dye Ingress Tests
Heinz Wolf, Tony Stauffer, Shu-Chen Y. Chen, Yoojin Lee, Ronald Forster, Miron Ludzinski, Madhav Kamat, Brian Mulhall and Dana Morton Guazzo; PDA Journal of Pharmaceutical Science and Technology September 2009, 63 (5) 489-498

Development of a Dye Ingress Method to Assess Container-Closure Integrity: Correlation to Microbial Ingress

Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies

Container Closure Integrity Testing—Practical Aspects and Approaches in the Pharmaceutical Industry
Vacuum Decay Test Cycle

The gold standard for test method reliability.

M5 Test Cycle

Cycle 1 (step 1 - 2)  
Large Leaks

Cycle 2 (step 3 - 5)  
Small Leaks

Test Cycle Pass
Large Leak
Small Leak
High Voltage Leak Detection (HVLD$_{mc}$)
This new technology applies less than **50% of the voltage** used with conventional high voltage technologies and the product it's exposed to less than a **5% of the voltage exposure** experienced when testing with comparable HVLD solutions.

\[
V(t) = V_m \sin(\omega t + \phi) \cdot t + \phi
\]
Good Sample

Leak

V – High Voltage Source
R – Electric Resistance of the product
C₁ – Capacitor 1: Glass between the inspection electrode and product
C₂ – Capacitor 2: Glass between the detection electrode and product
I₁ – current produced when product container is sealed
I₂ – current produced when product container is defective
High Voltage Leak Detection (HVLD\textsuperscript{mc})

![Diagram showing signal voltage over time with labels for good and defect conditions.]

**Inspection**

**Electrode**

- $C_1$
- $C_2$
- $R$
- Glass Wall
- Liquid Contents
- Glass Wall

**Detection Electrode**

**Graph:**
- Voltage vs. Time (0 to 3000)
- Defect and Good conditions

**Diagram notation:**
- $C_1$
- $C_2$
- R
- Glass Wall
- Liquid Contents
- Inspection Electrode

**Legend:**
- Good
- Defect
MicroCurrent HVLD - Benefits

Product HV Exposure

Ozone Creation

10 minutes test
Outside the product

<table>
<thead>
<tr>
<th></th>
<th>Conventional HVLD</th>
<th>MicroCurrent HVLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure Voltage (V)</td>
<td>7000</td>
<td>300</td>
</tr>
<tr>
<td>Ozone Production (ppm)</td>
<td>0.305</td>
<td>0.006</td>
</tr>
</tbody>
</table>
PTI’s Robotic Platform

- Highly flexible
- Indexing accumulator
- Adaptive handling or nested presentations
- Multi-format rapid changeover
- Modular concept throughout
- Defects preserved
- HVLD$^{mc}$ or Vacuum Decay
Advanced Applications

- Auto-injectors
- Cartridges
- Combination devices
- Complex geometries
MicroCurrent HVLD

- Liquid fill
- MALL Sensitivity (<1 micron)
- Low exposure voltage
- Dynamic product range
- No Ozone generated
- Defect position ID
- Detects clogged defects
- 0.2mL to 500mL containers

Vacuum Decay

- Small molecule liquid and lyophilized
- MALL Sensitivity (<1 micron)
- Large leak capture, no contamination
- Quantifies leak size
- Adaptive leak testing capabilities
- Any size container
Next Generation Sensitivity

Leak Detection Capability

![VeriPac 465](image)
Conclusions

- Dye ingress is not effective for many parenteral applications
- Understanding product and package dynamics is critical
- Next generation technologies: Reliability, Sensitivity, Practicality
- Robotic automation provides distinct advantages
- Vacuum Decay and HVLD are powerful technologies for parenteral CCIT

Uncompromised flexible quality assurance.
Thank you!

o.stauffer@ptiusa.com
Best Practices: CCIT In Manufacturing
A Webinar Series by PDA Asia Pacific
8 July 2020 (Wednesday)
10:00-11:00 hours (GMT+8)

How to Better Understand Automated Deterministic Inspection Technologies for Complete Quality Control of Prefilled Syringes

Oliver Stauffer
CEO of PTI - Packaging Technologies & Inspection
United States
Supplemental Slides
Tortuous Defects

- 30µ Pinhole – ~3.26 sccm
- 30µ 20mm Channel – ~0.16 sccm
- 30µ 40mm Channel – ~0.08 sccm
Proteinaceous product may interfere with defect detection.”¹

➢ Naturally occurring defects and laser defects are susceptible to blockage when testing.
➢ Solutes may be deposited internal to the defect passage during testing due to liquid vaporization.
➢ Pipettes draw liquid through the calibrated defect into the pipette cavity ahead of test.
➢ Volume of liquid exposed to vacuum with low potential for solute blockage before test.
➢ Ideal condition for detection.
➢ Not representative of naturally occurring defects.

### Statistical Quality Limits

<table>
<thead>
<tr>
<th>Reject Limit Set Point</th>
<th>% Known good will Pass</th>
<th>% Known good will Fail</th>
<th># of good samples that will fail per 10,000</th>
<th>1 False Reject Per</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg +1 Std Dev</td>
<td>84.13%</td>
<td>15.87%</td>
<td>1587</td>
<td>6</td>
</tr>
<tr>
<td>Avg +2 Std Dev</td>
<td>97.72%</td>
<td>2.28%</td>
<td>228</td>
<td>44</td>
</tr>
<tr>
<td>Avg +3 Std Dev (1x Noise)</td>
<td>99.87%</td>
<td>0.13%</td>
<td>13</td>
<td>769</td>
</tr>
<tr>
<td>Avg +4 Std Dev</td>
<td>99.99%</td>
<td>0.0033%</td>
<td>.33</td>
<td>31,574</td>
</tr>
<tr>
<td>Avg +5 Std Dev</td>
<td>99.9972%</td>
<td>0.000028%</td>
<td>.0028</td>
<td>~3,500,000</td>
</tr>
<tr>
<td>Avg +6 Std Dev (2x Noise)</td>
<td>99.999%</td>
<td>0.00001%</td>
<td>.001</td>
<td>~10,000,000</td>
</tr>
</tbody>
</table>

**Note:** The table above outlines the statistical quality limits for different reject limit points, showing the percentage of known good will pass, the percentage of known good will fail, the number of good samples that will fail per 10,000, and the 1 false reject per.
## Naturally Occurring Defects

<table>
<thead>
<tr>
<th>Sample</th>
<th>Leak Rate</th>
<th>Visual</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mbar·l/s</td>
<td>10⁻⁵ mbar·l/sec</td>
<td>sccm</td>
</tr>
<tr>
<td>1</td>
<td>0.00095</td>
<td>95</td>
<td>0.05700</td>
</tr>
<tr>
<td>2</td>
<td>0.0000021</td>
<td>0.21</td>
<td>0.00013</td>
</tr>
<tr>
<td>3</td>
<td>0.000014</td>
<td>1.4</td>
<td>0.00084</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0.00000</td>
</tr>
<tr>
<td>6</td>
<td>0.00067</td>
<td>67</td>
<td>0.04020</td>
</tr>
<tr>
<td>7</td>
<td>0.015</td>
<td>1500</td>
<td>0.90000</td>
</tr>
<tr>
<td>9</td>
<td>0.0000002</td>
<td>9</td>
<td>0.00002</td>
</tr>
<tr>
<td>10</td>
<td>0.00029</td>
<td>29.0</td>
<td>0.01740</td>
</tr>
<tr>
<td>11</td>
<td>0.074</td>
<td>7400</td>
<td>4.44000</td>
</tr>
<tr>
<td>12</td>
<td>0.053</td>
<td>5500</td>
<td>3.30000</td>
</tr>
<tr>
<td>16</td>
<td>0.0014</td>
<td>140</td>
<td>0.08400</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0.00000</td>
</tr>
<tr>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0.00000</td>
</tr>
<tr>
<td>20</td>
<td>0.018</td>
<td>1600</td>
<td>0.96000</td>
</tr>
</tbody>
</table>
Sample 3

He Certified Leak Rate

67.0 \times 10^{-5}\text{ mbar·l/s}

0.04020 \text{ sccm}

2.24 \text{ µm}

Sample 6

He Certified Leak Rate

29.0 \times 10^{-5}\text{ mbar·l/s}

0.01740 \text{ sccm}

1.47 \text{ µm}
<table>
<thead>
<tr>
<th>Sample</th>
<th>He Certified Leak Rate</th>
<th>He Certified Leak Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.21</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>$10^{-5}$ mbar·l/s</td>
<td>$10^{-5}$ mbar·l/s</td>
</tr>
<tr>
<td></td>
<td>0.00013 sccm</td>
<td>0.00084 sccm</td>
</tr>
<tr>
<td></td>
<td>0.13 ~µm</td>
<td>0.32 ~µm</td>
</tr>
</tbody>
</table>

10.0V

7.6V
MicroCurrent HVLD

Ozone Creation

Exposure Voltage

Product Range

Good Sample

Leak
Deterministic CCI

- A package’s ability to prevent product loss, maintain product sterility, and in some cases, prevent oxygen ingress or maintain sub-atmosphere headspace pressures.
- Not defined as absence of microbial ingress, liquid ingress, or loss of sterility.

**Deterministic**: the leakage event is based on phenomena that follow a predictable chain of events, and leakage is measured using physicochemical technologies that are readily controlled and monitored, yielding objective quantitative data.

**Deterministic methods**
- Electrical Conductivity and Capacitance (HVLD)
- Laser-Based Gas Headspace Analysis
- Mass Extraction
- Pressure Decay
- Tracer Gas Detection, Vacuum Mode
- Vacuum Decay