Container Closure Integrity: Regulations, Test Methods, Application

Test Methods: Fundamentals

Instructors
Brandon Zurawlow; Containsure; bz@containsure.com
Allison Dill, Ph. D.; Eli Lilly and Company; dillal@lilly.com

With significant contribution from Dr. Dana M. Guazzo PhD, RxPax, LLC, dguazzo@rxpax.com

Basel Switzerland, February 27 - 28, 2020

Outline

Test methods Fundamentals

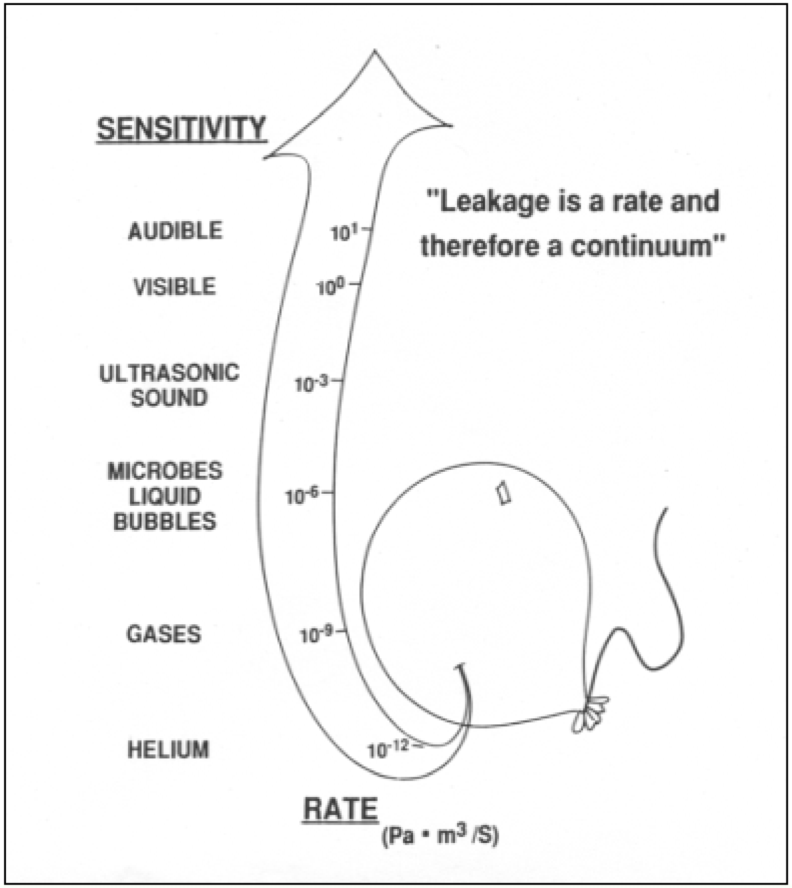
- CCI testing principles
- Leak and Positive controls
- Gas flow: flow rate & leak size
- Correlation between leak size (flow rate) and microbial contamination risk

CCI Testing Technology Overview

Most advanced CCIT technologies rely on gas flow

– more reliable (for micron-size leaks)

– More predictable, some are quantitative



Smallest leaks **only** allow
gas flow

Larger leaks **may also** allow
liquid flow

Largest leaks **may also** allow
microbial ingress

CCI Testing Technology Overview

Technology	Test Medium	Typical Challenge Condition	Response	Detection
Microbial Challenge	Liquid flow (Microbial species)	Pressure differential	Turbidity due to microbe growth	Visual
Dye ingress	Liquid flow (Dye solution)	Pressure differential	Dye presence	Visual or spectrophotometer
Vacuum Decay	Gas flow	Pressure differential	Pressure change	Pressure transducer
Mass Extraction	Gas flow	Pressure differential	Mass flow	Mass flow sensor
Headspace (e.g. oxygen) Analyzer	Gas flow (e.g. O2)	Partial pressure differential (e.g. O2)	Oxygen	Laser absorption spectroscopy
Helium Leak Detection	Gas flow (Helium)	Pressure differential	Helium	Mass spectrometer
High Voltage Leak detection	Electron flow (Current)	High voltage	Current (electron flow)	Current to voltage converter

CCI Testing Technology Overview

- Most CCIT technologies do not detect leak (defects) directly

- Instead, they detect presence of leak by monitoring the **biological and/or physiochemical responses** caused by a medium passing through the leaking path, typically driven by certain challenge conditions

- Technology detection performance depends on:
  - Test medium: Liquid (with microbe/dye tracer) v.s. gas
  - Challenge conditions: pressure differential, high voltage
  - Response detection methods

Leak and Leak Standards

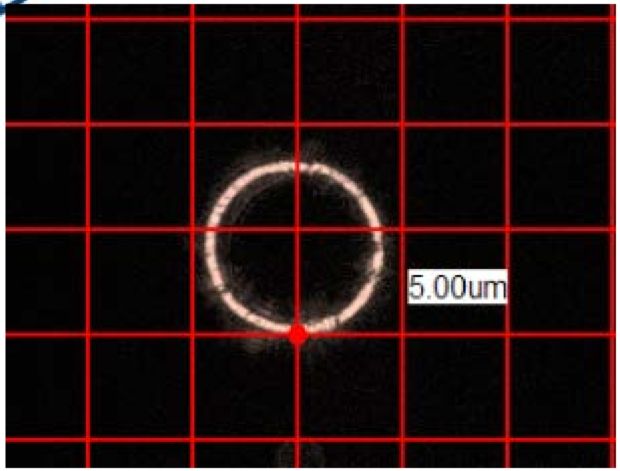
Leak

- A gap or breach in the container capable of permitting the passage of liquid or gas (Syn. “Leak path”)
- Real world leaks are usually complex, featuring various shapes, length, forms; some are transient and can change over time

Common Leak Standards (Positive Controls)

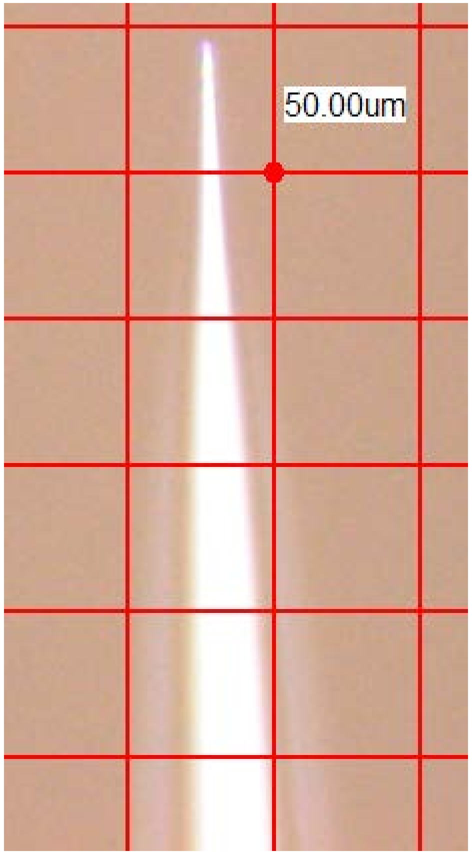
- Pulled Glass Capillary Tip (Micropipette)
- Glass Capillary Tube
- Laser drilled defect

Pulled Glass Capillary Tip (Micropipette)



Top View showing the tip orifice

Glass tube with the tip pulled into micron size capillary



Side View showing approximate length

Glass Capillary Tube

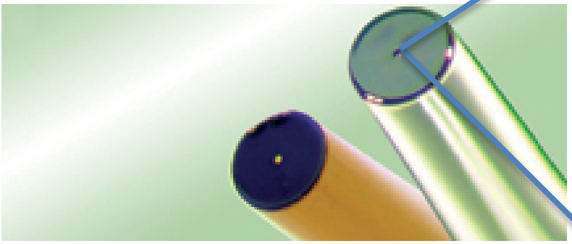
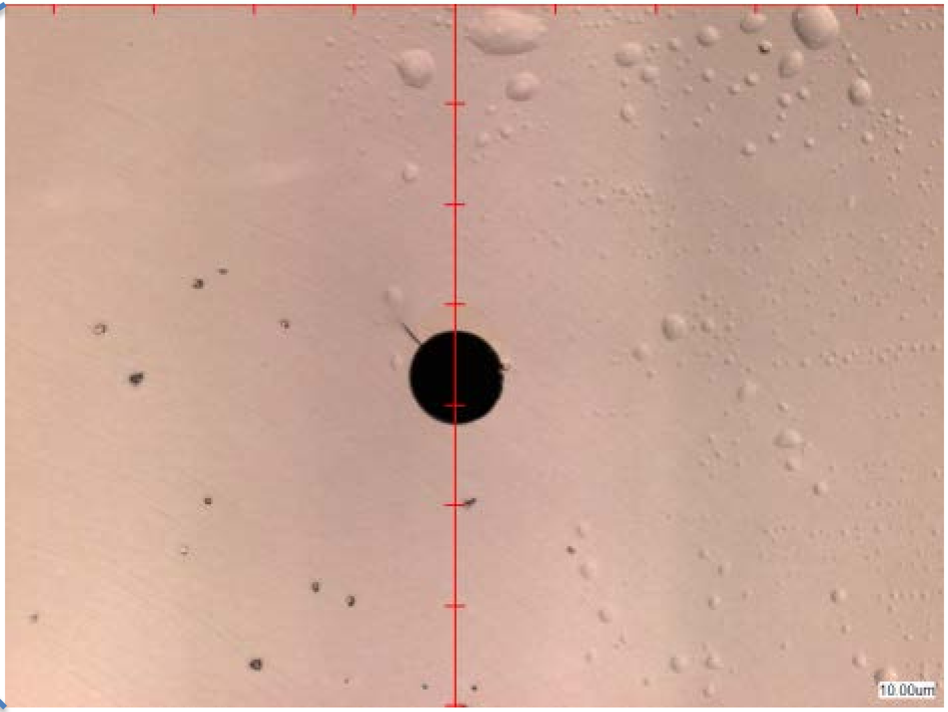
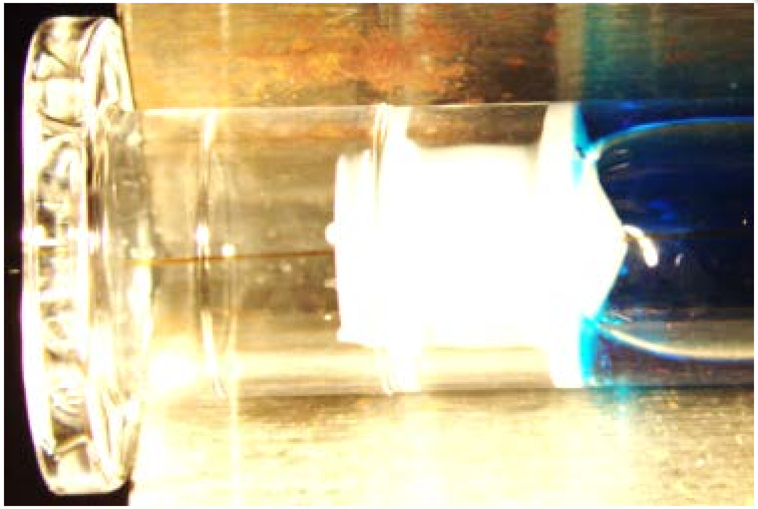


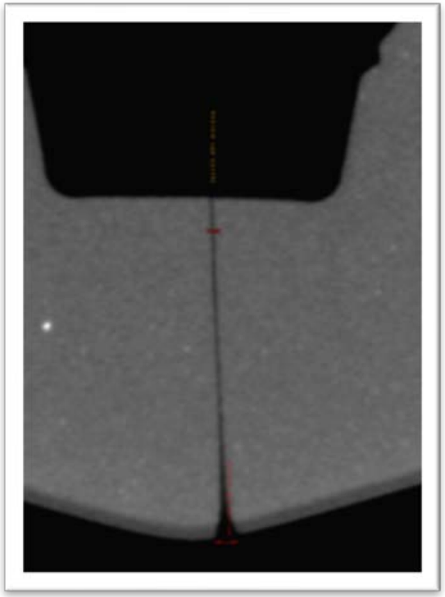
Image courtesy of Polymicro Technologies by Molex®

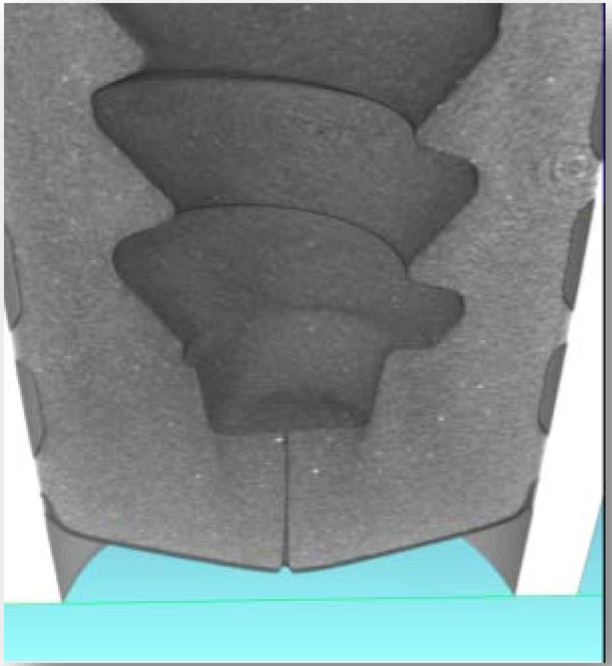




Uniform size through the length of the capillary tube

Laser Drilled Defect (Elastomer/Plastics)

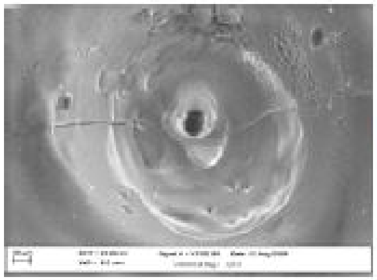




- Laser drilled defect can be readily created in plastics or elastomer materials
- Defect size may change upon applying stress on elastomer materials (e.g. insertion in syringe barrel)

Laser-drilled Defects in Glass

Glass Syringe Defects by Lenox Laser



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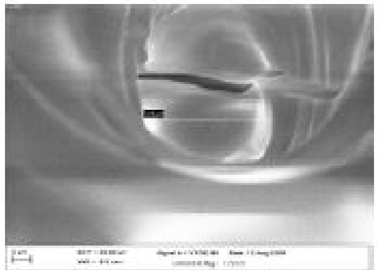

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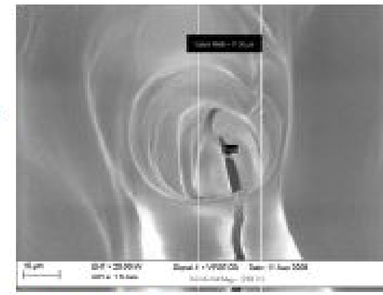
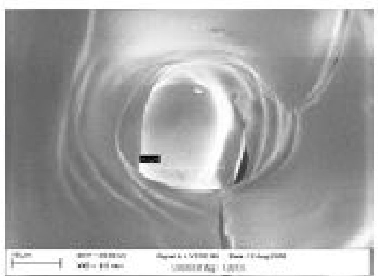
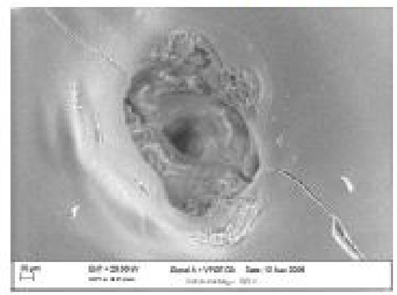


Nominal hole size 10 µm

107



Nominal hole size 5 µm



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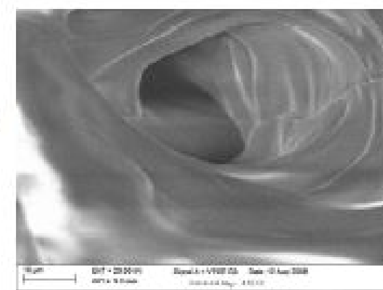


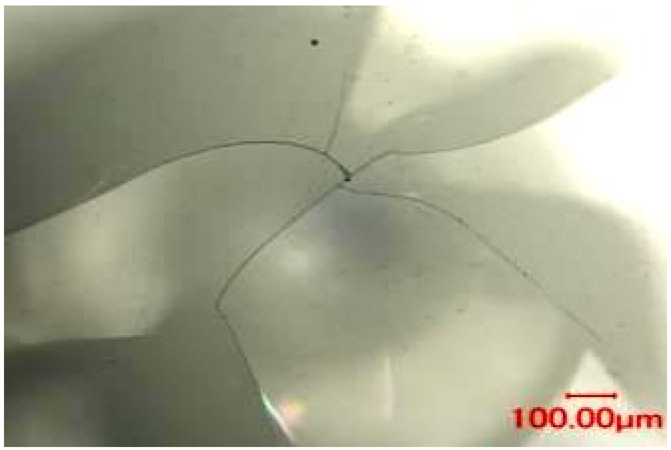
Nominal hole size 15 µm

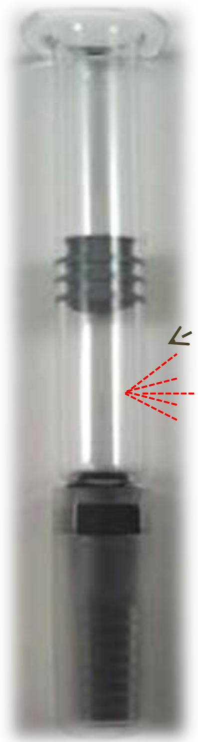
The laser-drilled defects in glass are not ‘ideal’ defects but realistic ‘tortuous path’ defects

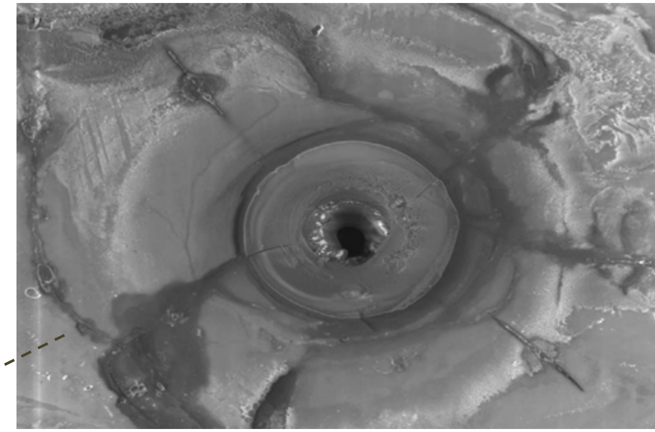
* Source: Dana Guazzo, presentation “Sterile Product Integrity Testing”, May 17, 2010

Laser Drilled Defect (Glass)

Example image of a laser drilled defect on the laser exit (i.e. glass interior surface)







Example image of a laser drilled defect on the laser entrance side (i.e. glass exterior surface)

LASER

- Laser drilled defects in glass are not well defined holes of a uniform size
- Some may be made to approximate “holes” while others may resemble a network of cracks – both are valuable as they represent specific types of “real-world” defects
- Know the laser drill processes and the defect characteristics

Which Type of Defect Should I use?

- Use positive controls that best resemble "real-world" defects of interest to demonstrate method effectiveness

Examples: to demonstrate the method is capable of detecting 10um defects

Defect Type of interest	Positive Controls (10um)
IV bag leaks caused by punctures/ abrasion	Laser drilled pinhole on the bag film with ~10um ID (measured by microscopic imaging)
Poor seals or micro-channels on the IV bag seams	10um capillary tube of similar length glued into the seam (the 10um ID can be microscopically verified)
Cracks in a vial glass wall (~2mm thick)	Laser drilled irregular glass defects, calibrated to be ~10um using gas flow rate per USP method

Characterization of Leaks

- Most industries uses leak flow rate to characterize a leak
  - Leak flow rate directly correlated to the material loss through the leak (e.g. compressed natural gas pipeline leaks)
  - Leakage Flow Rate is a measure of the rate of gas flow (mass or volume units) which passes through a leak path under defined conditions of temperature and/or absolute or partial pressure gradient of leaking matter that exists across the package barrier

- Gas leak flow rates are usually expressed in standard cubic centimeter per second (sccs) under standard conditions (temperature 273K, pressure 760 torr)
  - Other units are also widely used

Pascal Cubic Meter Per Second	Standard Cubic Centimeter Per Second	Millibar Liter Per second	Torr Liter Per Second
$Pa \cdot m^3 \cdot s^{-1}$	Std $cm^3 \cdot s^{-1}$ (Alternatively, sccs)	$mb \cdot L \cdot s^{-1}$	$torr \cdot L \cdot s^{-1}$
1	9.87 ($\simeq$ 10)	1.00×10^1	7.50

Jackson CN, Sherlock CN, Moore PO, Nondestructive Testing Handbook, 3rd ed. Vol 1 Leak Testing, American Society for Nondestructive Testing, Inc. 1998

“Sizing” Leaks

- “Leak size” is widely used in pharmaceutical industry as a key characteristic for leaks largely due to its close association with microbial ingress risk
- Dimensionally sizing natural “real-world” leaks is not always practical nor precise.
  - Leaks are commonly thought of as HOLES or CHANNELS. BUT, natural leaks are complex, multi-cavity, tortuous paths (rarely uniform)
  - Size alone does not fully define a “real-world” natural defect
- “Sizing”, although not a comprehensive and precise characterization of a defect, is still useful because it allows for a rough and simplified assessment of microbial ingress risks

Methods for “Sizing” Defects

1. Direct microscopic dimensional measurement
   - Usually applies to simple “regular” natural defects (e.g. pin holes on a IV bag film) or positive control defects (e.g. capillary tubes)

2. Calibration via gas leak flow rate measurement
   - Usually for complex “real-world” defects (e.g. glass cracks)
   - *A “nominal” size* can be obtained by comparing the gas flow rate of the defect against known leak standards (e.g. NIST-traceable leak standards)
     - Two types of leak standards are commonly used – need to specify
       1. Orifice (a pin-hole of known size with essentially no depth)
       2. Capillary (with known uniform ID and Length)

3. Calibration vis gas diffusion rate (or headspace changes) measurement
   - Gas diffusion and headspace composition modeling are usually acceptable

Sizing Based on Gas Leak Flow Rate
– Calibration using orifice leak standards

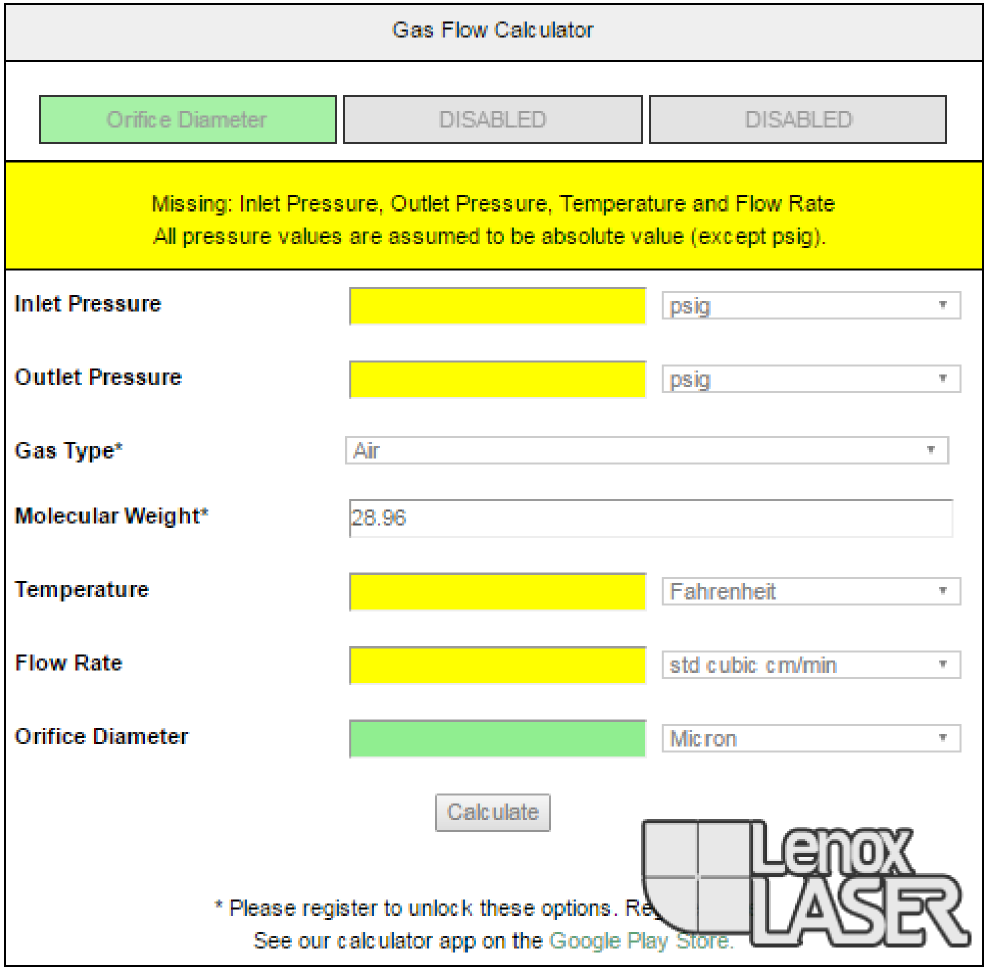
For orifice leaks (i.e. leaks with essentially no “depth”, a.k.a. sharp edge defects)

$$\textit{Flow Rate} \propto d^2$$

- Flow rate usually measured at a fully “chocked” conditions to simply the calculation
- Methodology is included in USP<1207>
- Nominal sizes can be easily calculated using the flow rate equation or online calculators

Calculator Examples

https://lenoxlaser.com/resources/calculators/orifice-calculator/



Gas Leak Flow Rate v.s. Orifice Size

USP <1207> presented:

Row	Air Leakage Rate[a] (stdcm^3/s)	Orifice Leak Size[b] (µm)
1	<1.4 x E-6	<0.1
2	1.4 x E-6 to 1.4 x E-4	0.1 to 1.0
3	>1.4 x E-4 to 3.6 × E-3	>1.0 to 5.0
4	>3.6 x E-3 to 1.4 × E-2	>5.0 to 10.0
5	>1.4 x E-2 to 0.36	>10.0 to 50.0
6	>0.36	>50.0

[A] Dry air leakage rate measured at 1 atm differential pressure across an orifice leak (i.e., leak inlet pressure of 1 atm versus outlet pressure of approximately 1 Torr) at 25 . The theoretical correlations of orifice sizes to air leakage rates were provided by Lenox Laser, Glen Arm, MD. Leakage rates are approximation ranges.

[B] Nominal diameter orifice sizes assume a leak path of negligible length. Orifice sizes are approximation ranges.

Sizing Based on Gas Flow Rate
– Calibration using capillary leak standards

For defects with significant length (L)

Gas Flow Model EXAMPLES

- Hagen-Poiseuille viscous flow (barometric, shallow vacuum)

$$Q = \frac{128}{\pi}\frac{d^4}{L} \times \frac{P_{IN} - P_{OUT}}{\mu}$$

- Knudsen model for molecular flow (small defects, hard vacuum)

$$\dot{m} = \frac{\pi d^3}{\sqrt{2RT}} * \frac{P_{IN} - P_{OUT}}{L}$$

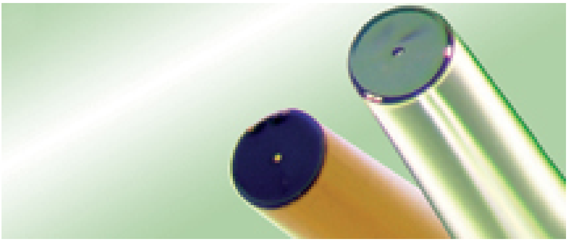
P_{in}-pressure inside package; P_{out}-pressure inside chamber; μ-Viscosity ;T-temperature;R-Specific gas constant

Flow (Q-volumetric flow, mass flow)

= f (**d**, Length, Pin, Pout, T)

Kept constant

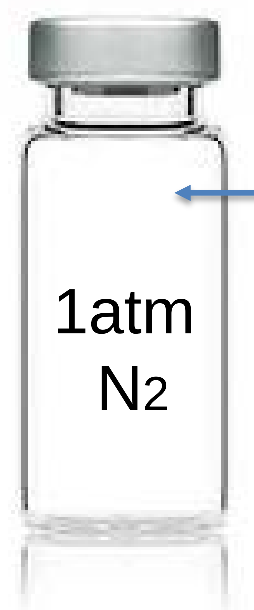
- Nominal sizes can be readily obtained experimentally by comparing flow rates of samples against those of known capillary standards (preferably of similar length L)



Courtesy of Hemi Sagi, ATC-Pfeiffer

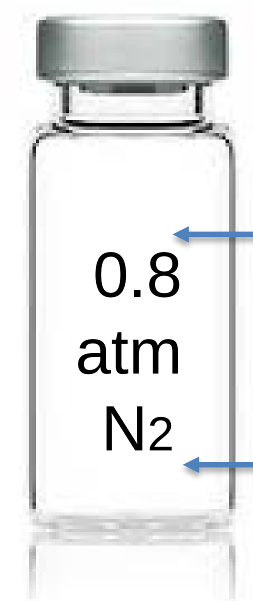
Sizing Based on Headspace Changes

1atm air (79%N_2; 21% O_2)



Diffusion (driven by N_2 partial pressure differential)

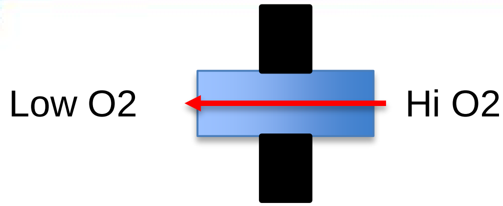
1atm air (79%N_2; 21% O_2)



Air flow (driven by absolute pressure differential)

Diffusion

Sizing Based on Gas Diffusion Rate
(or Headspace Gas Concentration Change)



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

Fick's 1st Law

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."

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

The change in oxygen will be exponential with respect to time

$$\mathrm{P}_{oxygen}(t) = 20.9\%\left(1 - \exp(-\alpha t)\right)$$

Ingress Rate

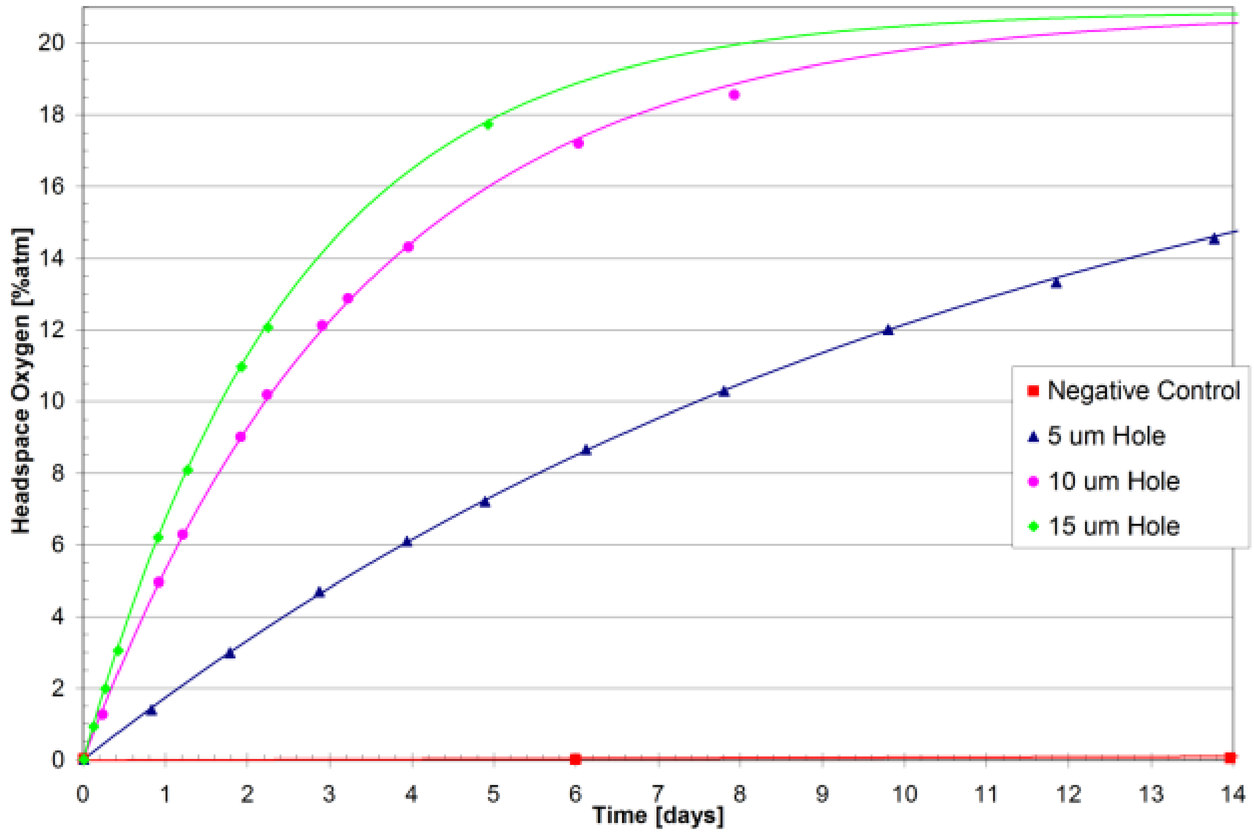
$$\alpha = \frac{D \cdot A_0}{l \cdot V} \left[s^{-1}\right]$$

The Ingress Rate is a function of the Diffusion Coefficient, the container Volume and the defect cross-sectional Area and Depth

D. Duncan, Lighthouse Instruments

Example: Headspace Oxygen% v.s. Leak Size

The linear regression fit (RSQ) for each line was 0.99 or higher for each set of data



Laser-drilled holes in thin metal plates are well-defined defects. They can therefore be used to generate 'calibration data' for gas ingress dynamics through a defect into a container.

D. Duncan, Lighthouse Instruments

Reporting Leak Size

- "Nominal" size – a useful tool for communication with key stakeholders (e.g. business leaders, regulatory agency microbiology reviewers)

- Many methodologies can be used to "size" a leak – the resultant nominal sizes may not in full agreement

  - No consensus methodologies haven bee established yet

- When stating leak sizes (or reporting package integrity), it is important to **define the measurement approach – Be transparent!**

Examples: Reporting Leak Size

Example 1. An intentional leak size-certified in gas flow rate terms.

A laser-drilled hole = 10.3 µm, certified that the air flow rate through this defect matches that of a same diameter pre-drilled hole in a thin metal plate measured at defined pressure and temperature conditions.

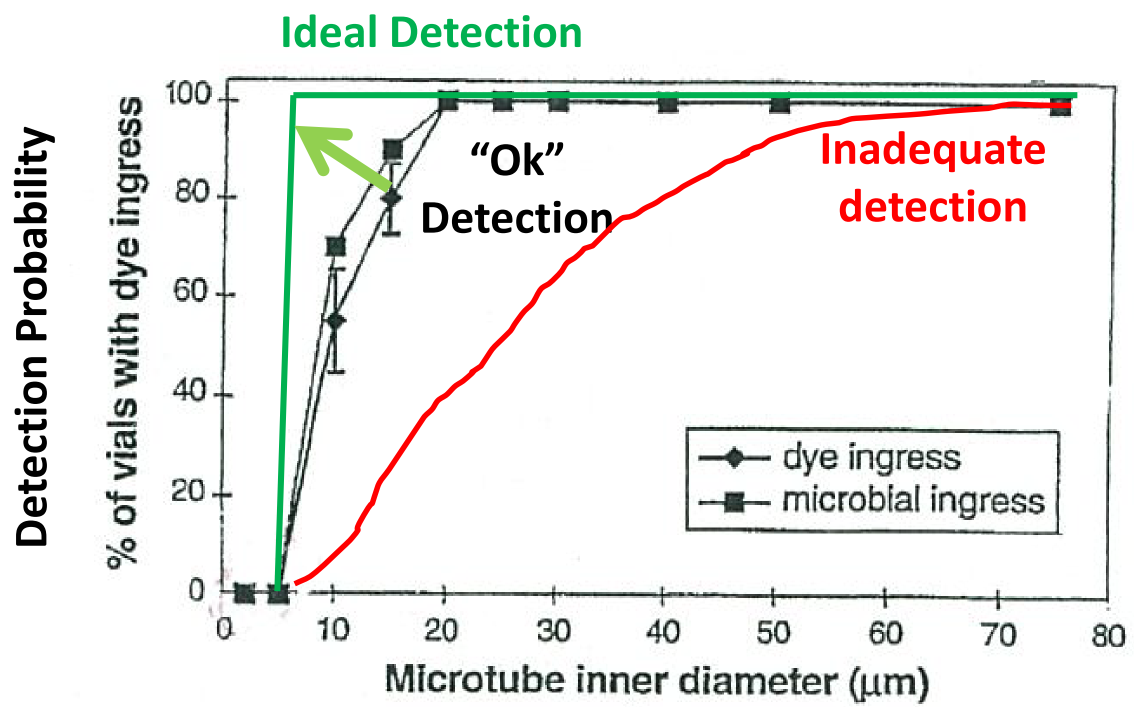
- *Comment: this statement indicates that the intentional leak sample is characterized using USP 1207 methodology and therefore is suitable for use as a positive control in method development and validation studies*

Example 2. Unintentional leak(s) directly sized in gas flow rate terms.

A test package containing 100% helium (flooded prior to closure) demonstrated a helium leak rate of 1 x 10-7 mbarL/s, when tested using a helium mass spectrometer, at 1 atmosphere differential pressure and ambient temperature.

- *Comment: this statement indicates that resultant helium leak rate is obtained using the identical methodology by Lee Kirsch as referenced in USP 1207. Therefore, the measured leak rate can be directly compared against the MALL to demonstrate container integrity.*

Detection of Leaks Critical to Microbial Ingress



Burrell L. S., et. al. PDA J Pharm Sci Tech 54, 449-455