Container Closure Integrity: Regulations, Test Methods, Application

Test Methods: Fundamentals

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Outline

Test methods Fundamentals

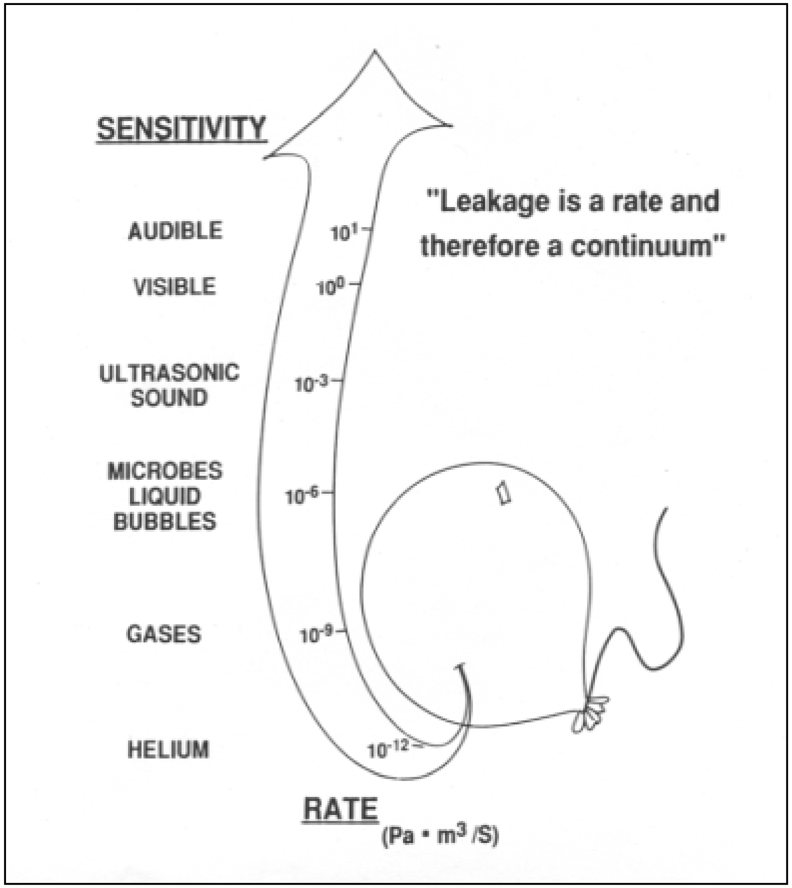
- CCI testing principles
- Leak and Positive controls
- Gas flow: flow rate & leak size
- Correlation between leak size (flow rate) and microbial contamination risk

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

A gap or breach in the container capable of permitting the passage of liquid or gas

Syn. “Leak path”

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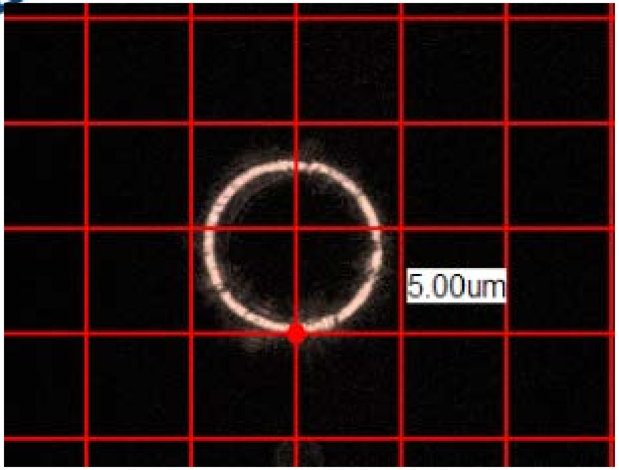
Real world leaks are usually complex, featuring various shapes, length, forms; some are transient and can change over time.

Common Leak Standards (Positive Controls)

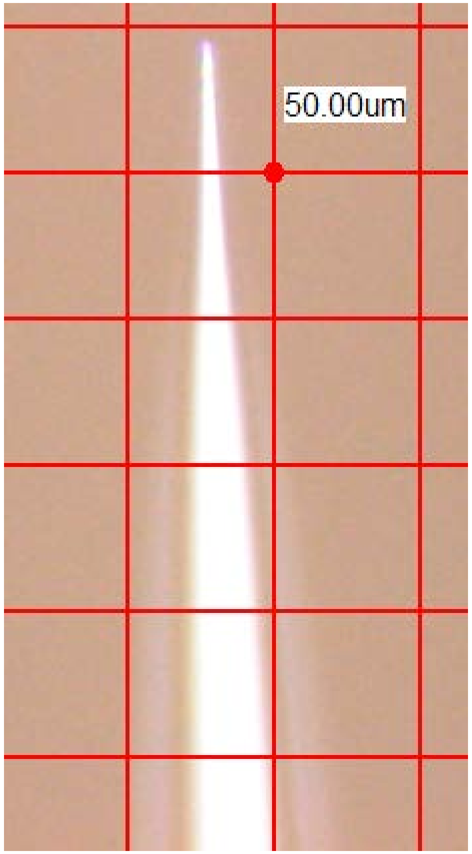
- **Pulled Glass Capillary Tip (Micropipette)**
- **Glass Capillary Tube**
- **Laser drilled defect**

Pulled Glass Capillary Tip (Micropipette)



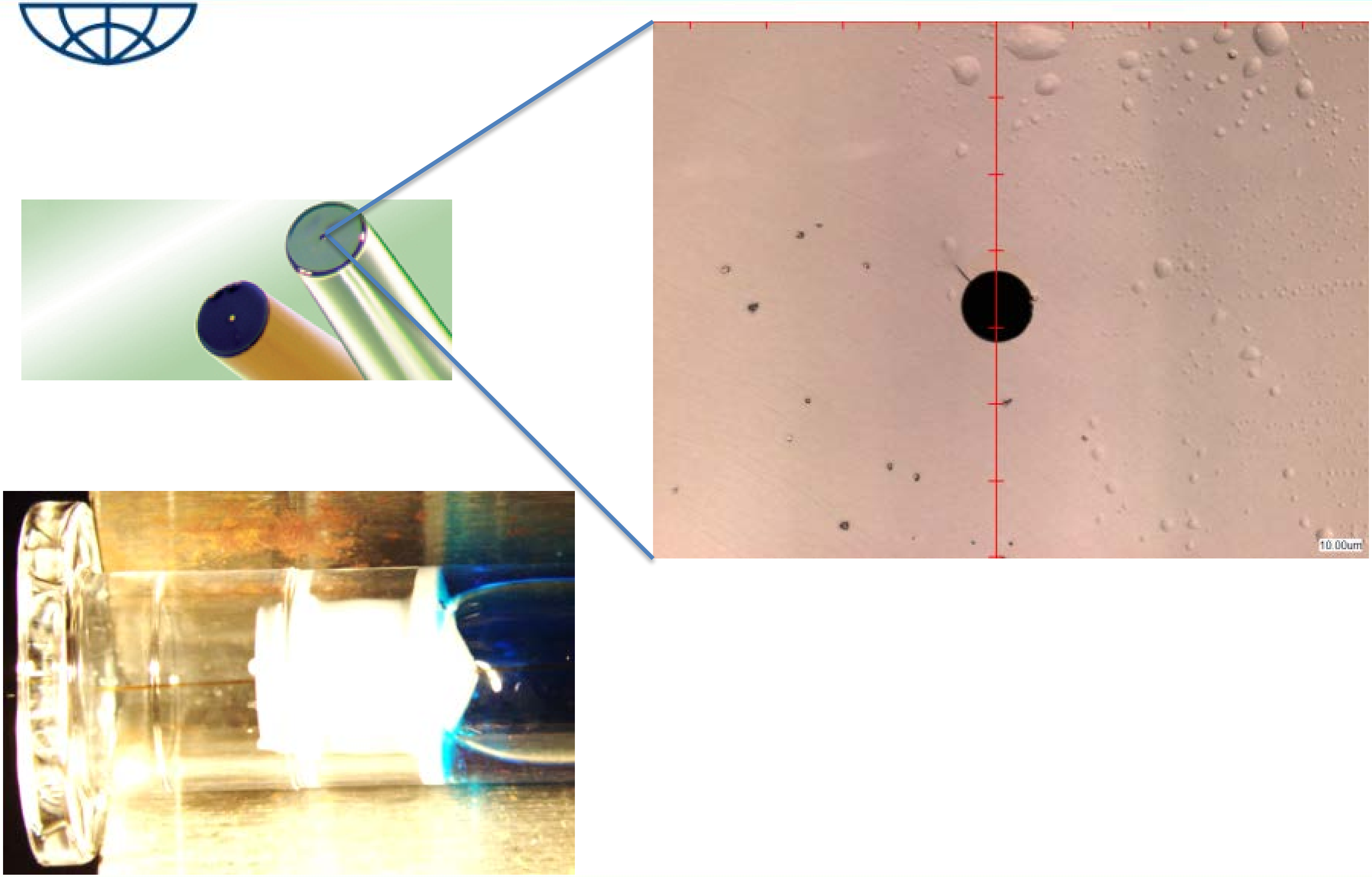
Top View showing the tip orifice

Glass tube with the tip pulled into micron size capillary

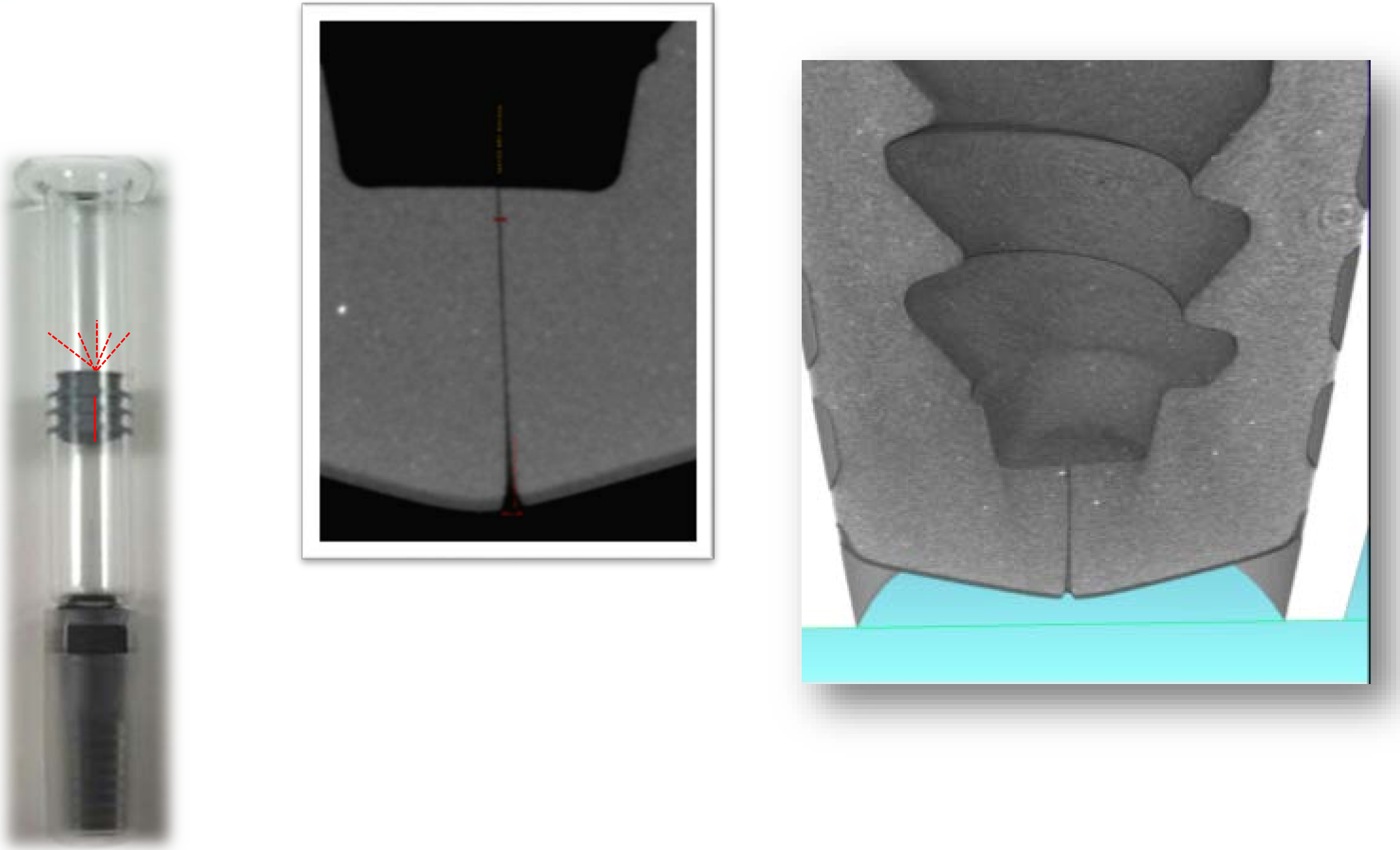


Side View showing approximate length

Glass Capillary Tube

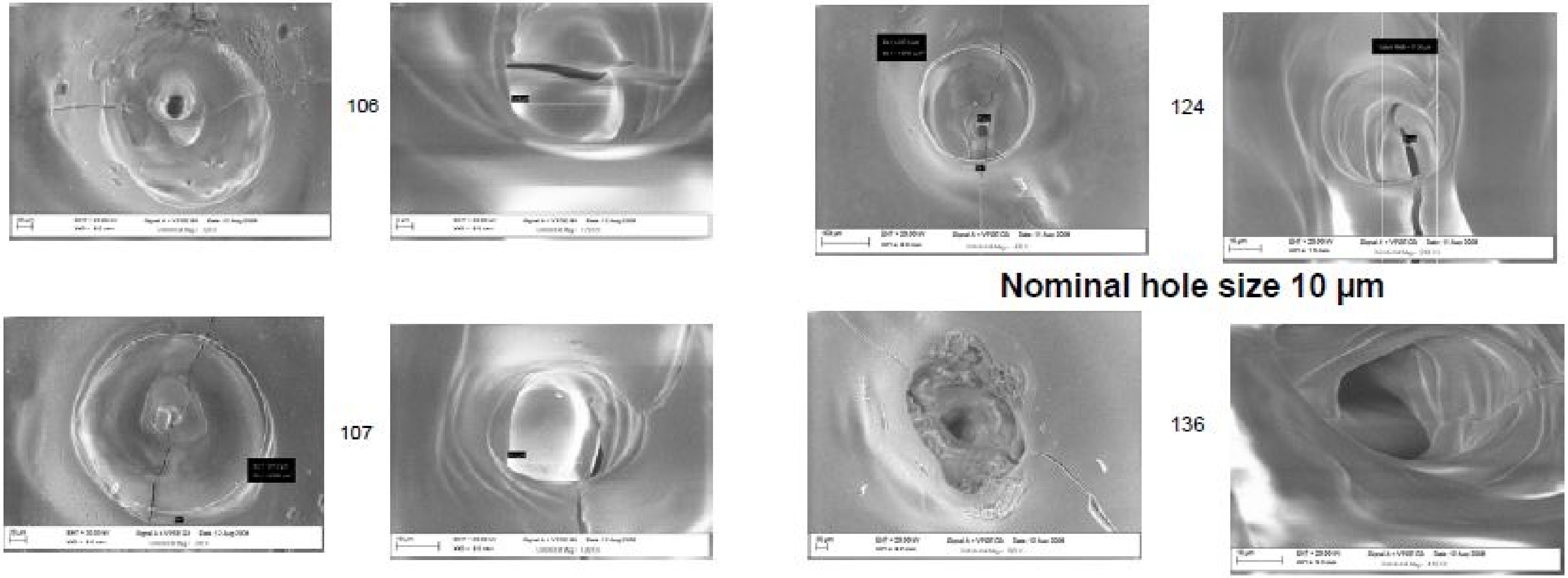


Laser Drilled Defect (Elastomer/Plastics)



Laser-drilled holes in glass containers

Glass Syringe Defects by Lenox Laser



Nominal hole size 10 µm

Nominal hole size 5 µm

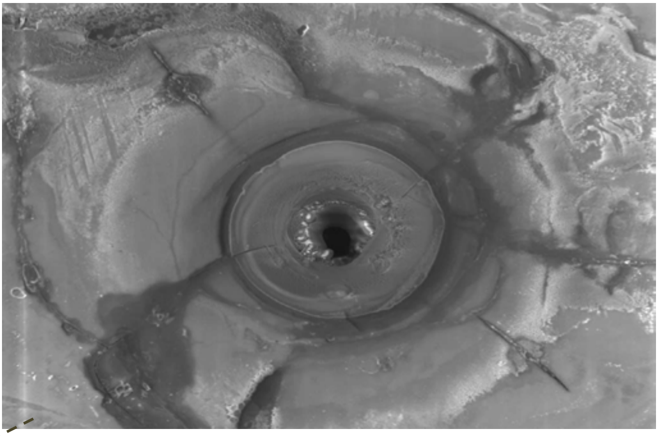
Nominal hole size 15 µm

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

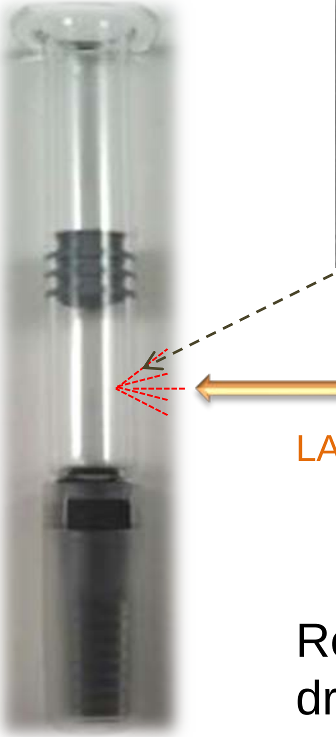
The laser-drilled defects in glass are not ‘ideal’ defects but realistic ‘tortuous path’ defects

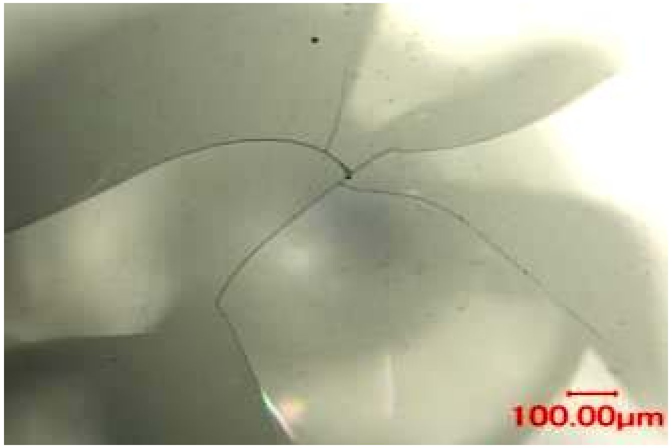
D. Duncan, Lighthouse Instruments

Laser Drilled Defect (Glass)



Laser Entrance
(exterior surfface)





Laser Exit (interior surface)

Recent advancements in laser drilling technology can produce relatively well defined “holes” through glass materials

Leakage Flow Rate

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

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Most industries uses leak flow rate to characterize a leak because it directly correlated to the material loss through the leak (e.g. compressed natural gas pipeline leaks)

Leakage Units

Standard temperature (273K), pressure (760 torr)

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

Leak Size

Leaks are commonly thought of as <u>HOLES</u> or <u>CHANNELS</u>

Leak size is widely used in pharmaceutical industry as a key characteristic for leaks largely due to its close association with microbial ingress risk

- BUT, natural leaks are **complex, multicavity, tortuous paths (<u>rarely uniform</u>)**
- Even laser-drilled defects (aka 'holes') are irregular
- Dimensionally sizing natural leaks is not practical.

Size Characterization Methods

Microscopic dimensional measurement

- ❑ Simple “regular” defects (e.g. pin holes on a IV bad film)

Gas leak rate measurement (under absolute pressure differential)

- ❑ Usually for complex “real-world” defects (e.g. glass cracks, fiber interference b/w plunger and barrel)
- ❑ *A “Nominal” size* can be obtained by comparing the gas flow rate of the sample against those from known leak standards
  - ▪ Meant to provide a simplified common scale to compare various defects
  - ▪ 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)

Gas diffusion rate measurement (under partial pressure differential)

- Alternatively, headspace composition change rate

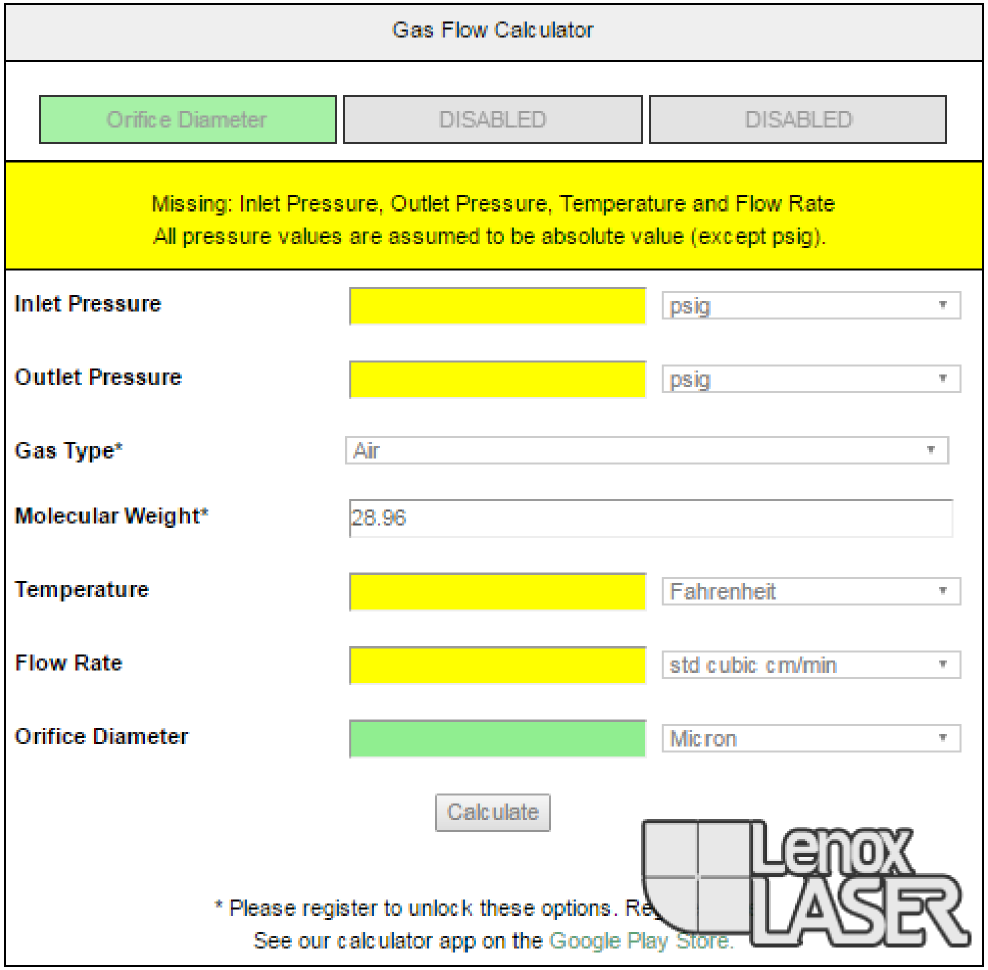
Orifice Flow Rate Calculation

$Flow\ Rate \propto d^2$

- 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/



Missing: Inlet Pressure, Outlet Pressure, Temperature and Flow Rate
All pressure values are assumed to be absolute value (except psig).

Inlet Pressure		psig
Outlet Pressure		psig
Gas Type*	Air	
Molecular Weight*	28.96	
Temperature		Fahrenheit
Flow Rate		std cubic cm/min
Orifice Diameter		Micron

* Please register to unlock these options. Re
See our calculator app on the Google Play Store.

Gaseous leakage rate as a function of orifice leak size (ref: USP <1207>)

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.

Capillary Flow Rate Calculation

At a given test condition- Flow measurement is function of defect geometry (or Equivalent Micro-Geometry, EMG):

EXAMPLES:

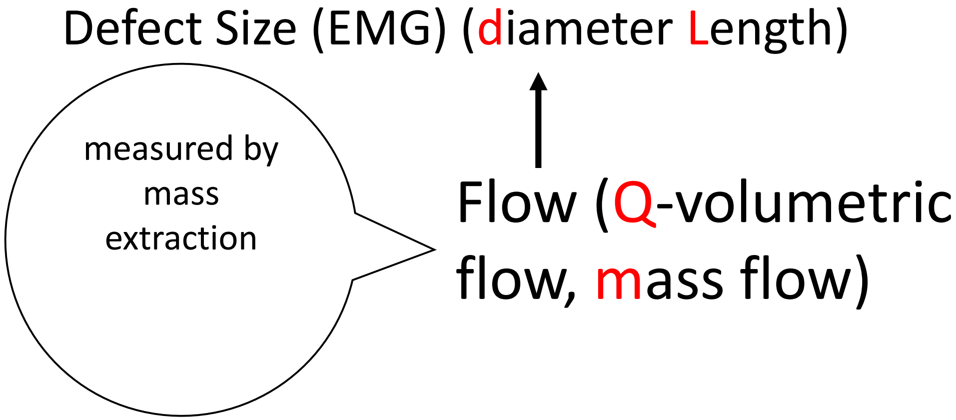
Hagen-Poiseuille viscous flow (barometric, shallow vacuum)

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

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



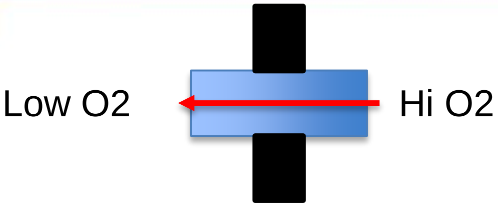
Defect Size (EMG) (diameter Length)

measured by mass extraction

Flow (Q-volumetric flow, mass flow)

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

Gas Diffusion Rate



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

Fick's 1st Law

New USP <1207> states:
“Mathematical models appropriate to leak flow dynamics may be used to predict the time required for 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

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

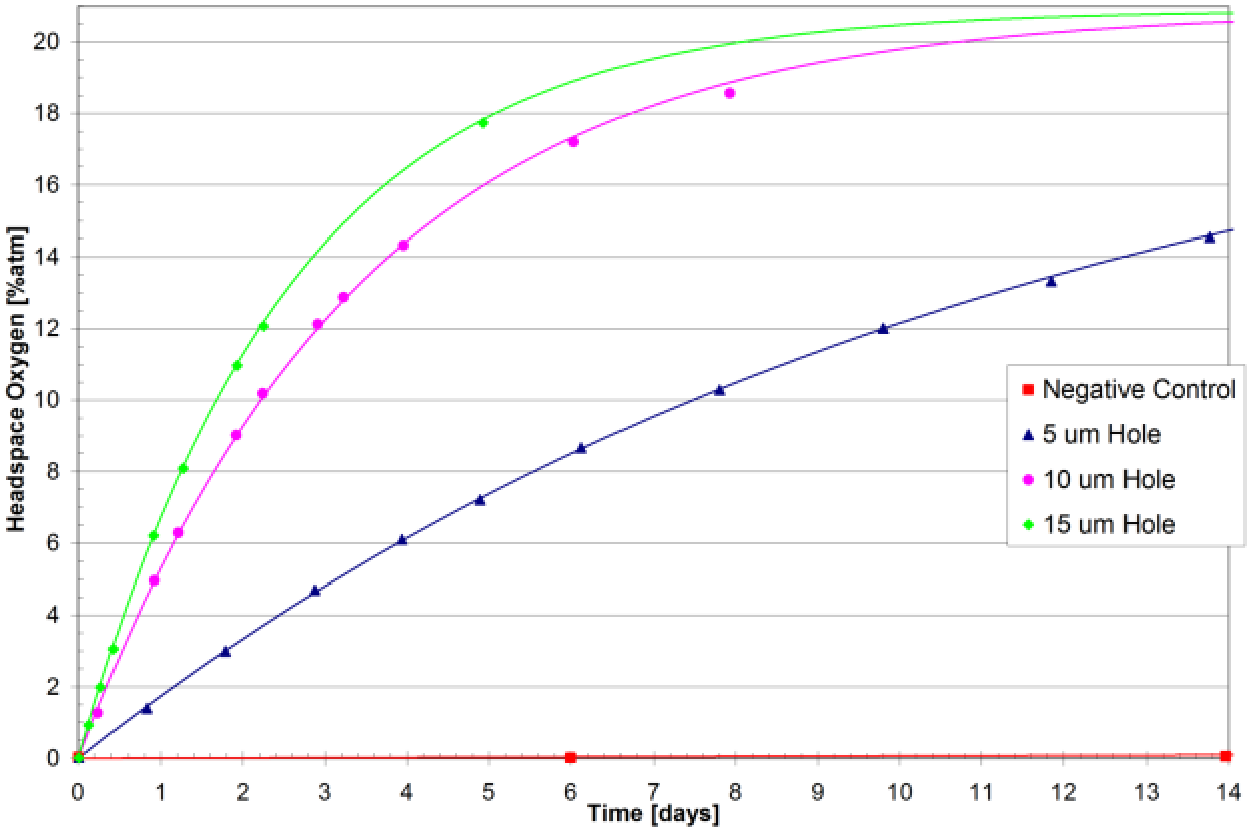
Ingress Rate

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

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

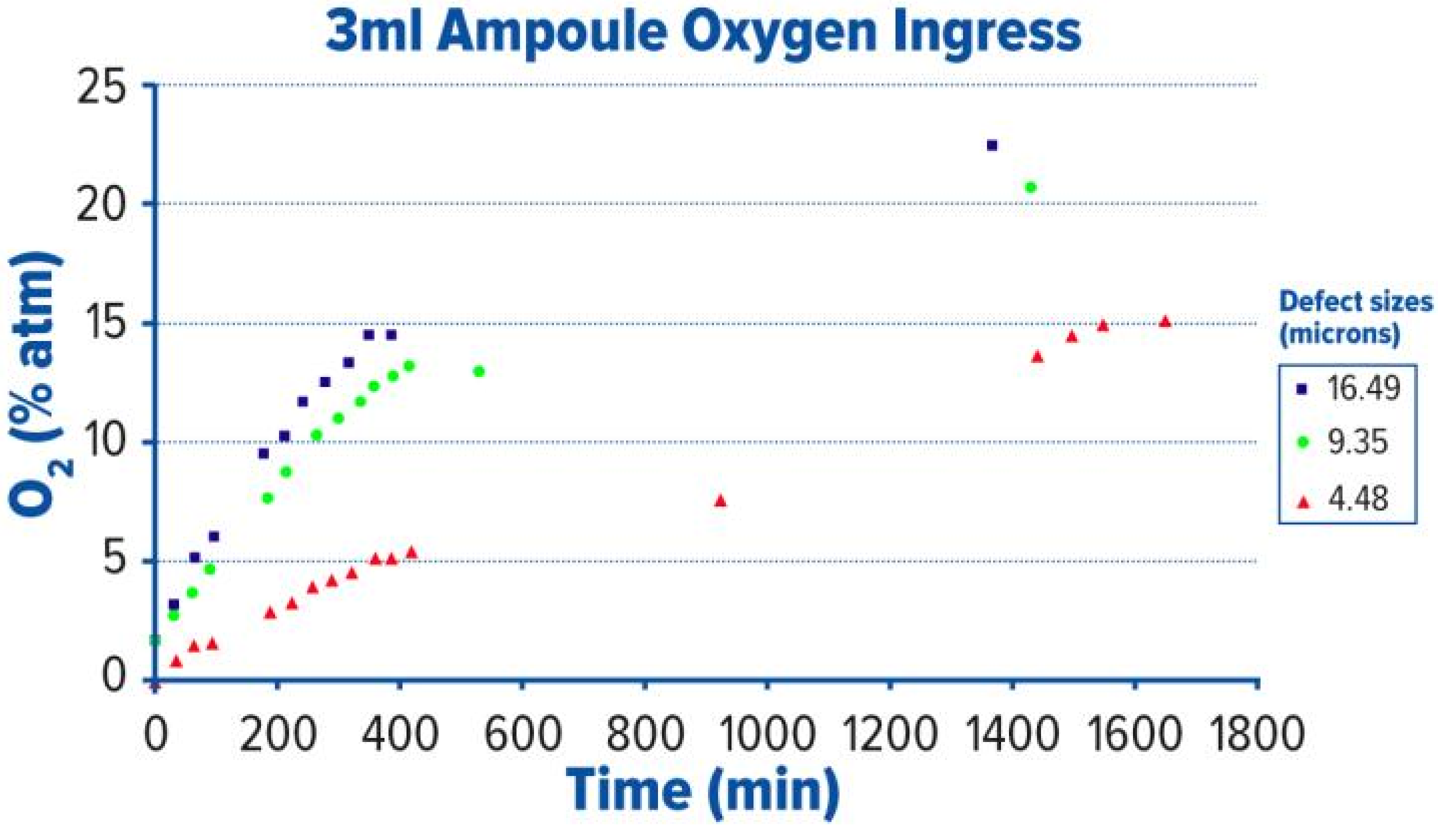
The change in the partial pressure of headspace oxygen versus time

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.

Gas ingress through laser-drilled holes



Natural gas ingress (diffusion or effusion) through the defects into the container headspace can be accurately measured as a function of defect size

Reporting Leak Size

When stating leak sizes (or reporting package integrity) it is important to **define the measurement approach.**

Example 1.

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

Such as, 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

Reporting Leak Size

Example 2.

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

Such as, 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.

Reporting Leak Size

Example 3.

Package leakage reported as the change in headspace over time.

Such as, a product requires nitrogen headspace at ambient pressure

No absolute pressure gradient; only O_2 partial pressure gradient

Leakage of O_2 into package is diffusional, from high to low concentration

Integrity evaluation can be measured by monitoring the rise in O_2 in the package over time =

Leakage rate of oxygen into package

+ Permeation of oxygen through package (may be significant)

Reporting Leak Size

Example 4.

Package leakage reported as the change in headspace over time.

- **Such as, a product requires a headspace of low absolute pressure**
- **Gas leakage into package is more rapid (convective flux), from higher pressure to lower pressure**
- **Permeation is relatively insignificant**
- **Integrity evaluation can be measured by monitoring the rise in absolute pressure in the package over time**

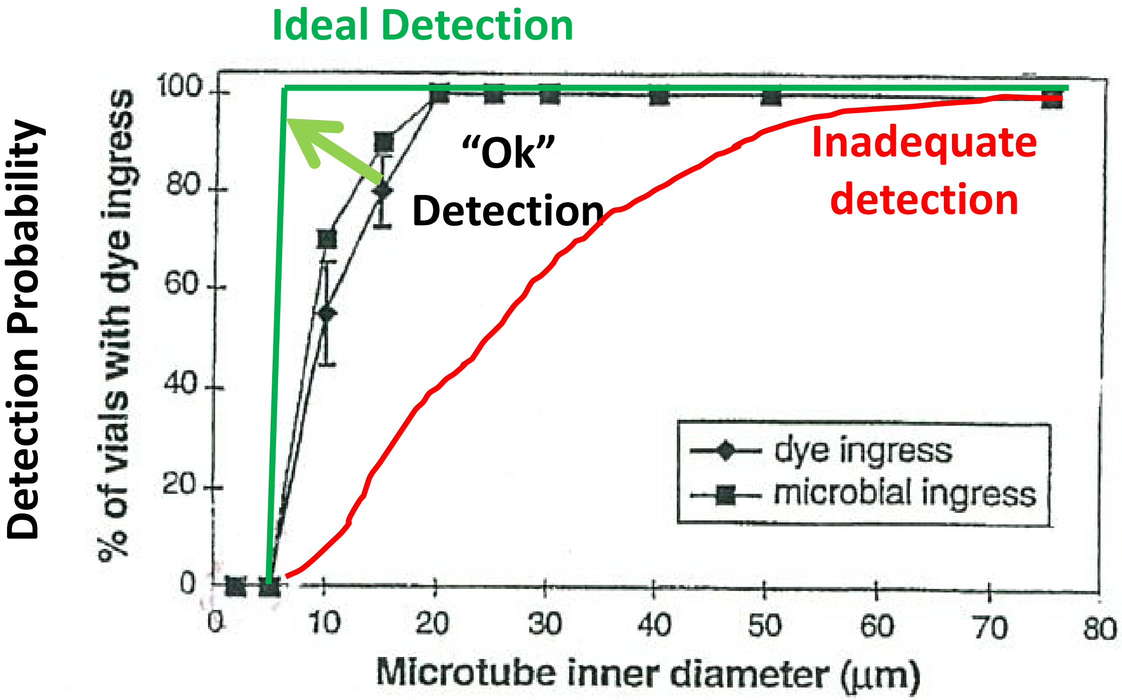
Reporting Leak Size

Example 5.

Package leakage reported as the absence of all leaks larger than the leak test method's limit of detection.

- **Such as, a liquid product is contained in a package in which liquid leakage, not gas, is a concern**
- **As all sterile product packages must prevent liquid leakage, liquid leakage ABSENCE, not RATE, is important**
- **Integrity can be reported as the absence of liquid tracer leakage. E.g., The test method used is validated as detecting 5 µm laser-drilled holes, tested at conditions of …..**
- **(Reporting the absence of leaks larger than LOD also applies to other methods such as microbial challenge, HVLD tests.)**

Detection of Leaks Critical to Microbial Ingress



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

Which one do I use?

- Use positive controls and leak size reporting most relevant to “real-world” defects of interest to demonstrate method effectiveness
- Examples: to demonstrate 10um detection capability

Real-world Defect of interest	Positive Controls (10um)	Reporting
IV bag leaks caused by punctures/ abrasion	Laser drilled pinhole on the bag film with ~10um ID	Microscopic imaging • Should be close to the “nominal size” as calculated per USP<1207>
Poor seals around IV bag seams	10um capillary tube of similar length glued into the seam	Microscopic imaging • also provide the “nominal size” per USP<1207> calculation as a reference
Cracks in a vial glass wall (~2mm thick)	Laser drilled irregular glass defects, calibrated to be ~10um using gas flow rate per USP method	Gas flow rate and the “nominal size” per USP<1207> • the “nominal size” using the flow rate v.s. leak size calibration curve constructed from 2mm-long capillary tubes of various sizes?