

Artificial Leaks / Positive Controls

Artificial Leaks

- Artificial leaks are required in order to assess CCIT method capability to detect a leak
- Artificial leaks are required in order to act as positive controls
- Artificial leaks do not necessarily simulate actual defects due to the irregular shapes and pathways found in container closure systems
- High variability among artificial leaks based on method used to create leaks
- Difficulty relating artificial leaks to leak size
- No gold standard – each approach has advantages and disadvantages
 - Laser drilling
 - Mircon wire
 - Micropipettes
 - Capillaries

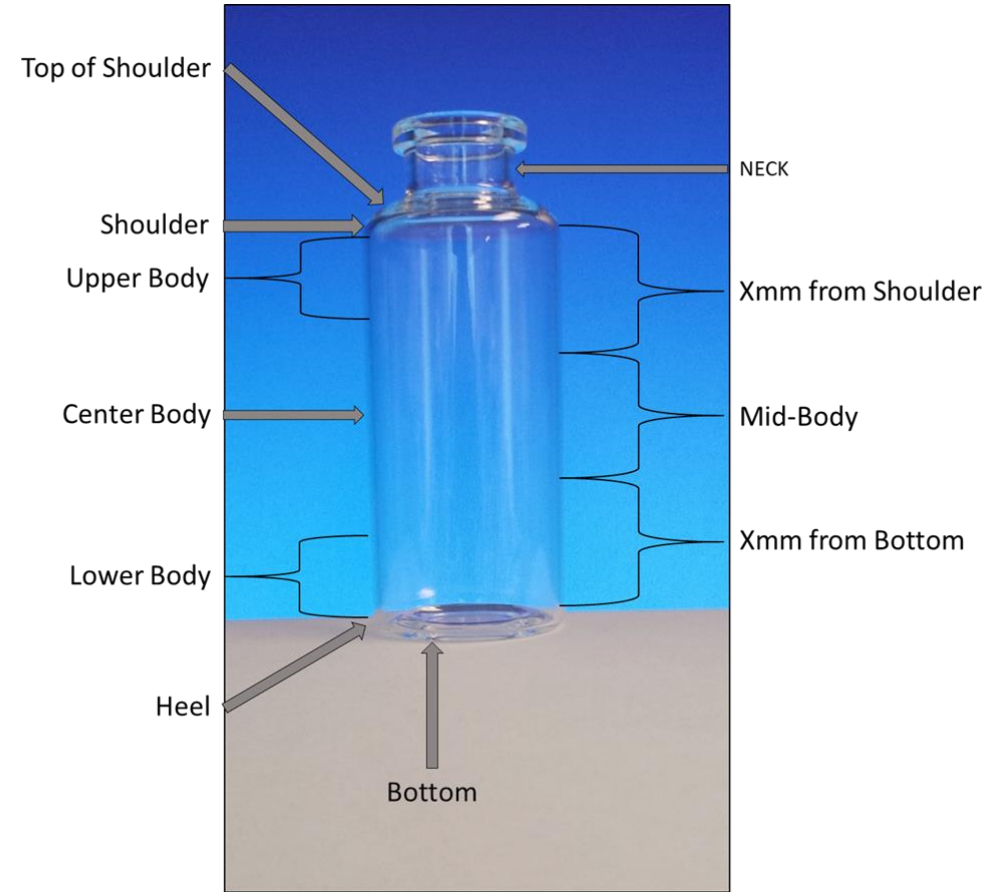
Leak Type	Advantages	Disadvantages	Experiences
<p>Mirco-pipettes, $\geq 0.1 \mu\text{m}$ ID (e.g. glass)</p>	<p>Easy sample preparation</p>	<ul style="list-style-type: none"> • Fragile & broken tips may not be detected • Difficult to determine hole size • Difficult to handle 	<ul style="list-style-type: none"> • Too fragile for routine use • High risk of false sensitivity • Need complete seal around micropipette • Silicone oil can clog • Pinhole type defect • Material matches primary container if glass is used
<p>Laser-drilled holes, $\geq 0.5 \mu\text{m}$ ID</p>	<ul style="list-style-type: none"> • Wide range of sizes • Better resembles natural defects (cracks in glass; pinholes in polymer) • Newer techniques allow for defined holes; fewer cracks 	<ul style="list-style-type: none"> • Cost • Size of laser-drilled void needs to be calibrated and represents defined path • Small hole can clog (silicone, viscous liq) • Holes can increase in size (temp changes, tension) • Variability in sizes depending on material/ wall thickness • Irregular shapes • Cannot be prepared on product 	<ul style="list-style-type: none"> • Risk of alteration post manufacture/calibration • Specialized external supplier • Many material can be drilled • Closer to real world defects • May reuse positive controls • Dirt or particulates could impact quality of holes

“Container Closure Integrity Testing – Practical Aspects and Approaches in the Pharmaceutical Industry” PDA J. Pharma. Sci. Technol. 2017 Mar-Apr;71(2):147-162

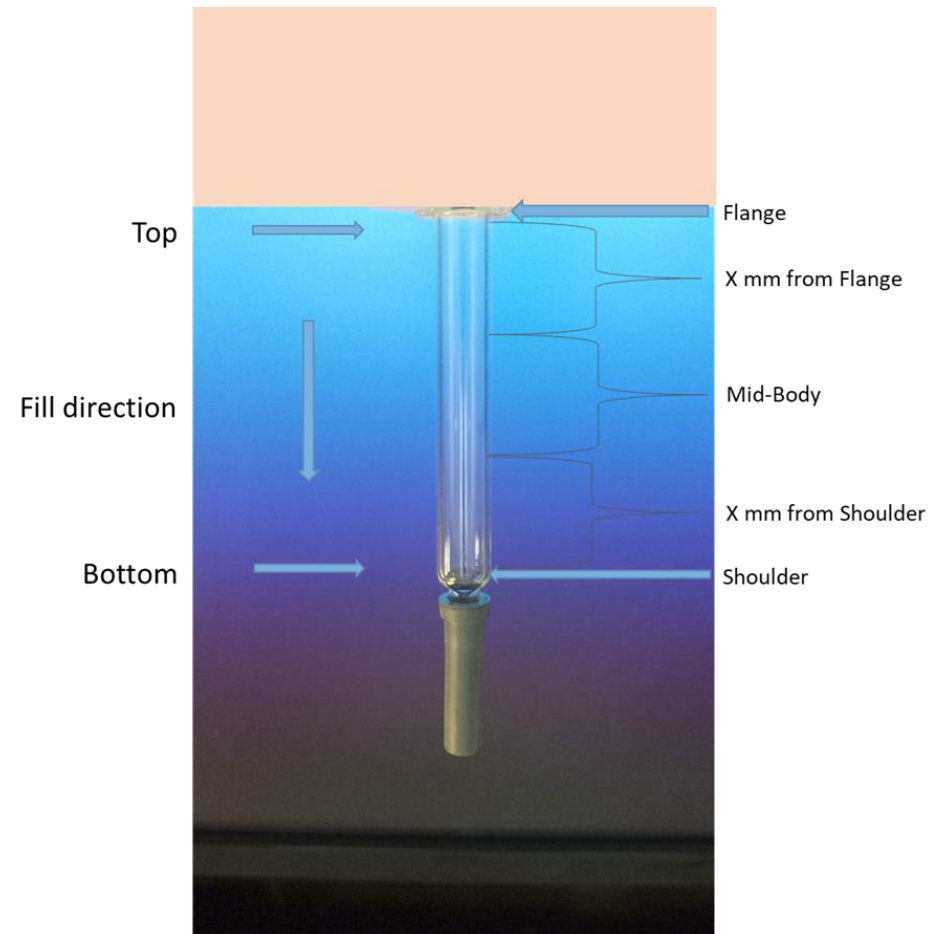
Leak Type	Advantages	Disadvantages	Experiences
Capillaries, $\geq 0.2 \mu\text{m}$ ID (e.g. fused silica)	<ul style="list-style-type: none"> • Robust • Easy preparation at testing location • Possible to prepare controls in specific packaging format and for multiple products • Prepared in flexible way (e.g. may contact liq and headspace) 	<ul style="list-style-type: none"> • Length of microtube defects is usually longer than real world defects • Typically nominal diameters $> 2\mu\text{m}$ available & uncertainty of actual diameter • Capillary diameter and hold diameter not comparable with regard to flow rate • Glue can create blockage 	<ul style="list-style-type: none"> • Robust, wide size range & different materials available • Leakage rates can be fine-tuned through length of capillaries; not only using IDs • Consistent dimensions/leaks • Defined dimensions mean don't have to calibrate each lead
Micron wires, $\geq 10 \mu\text{m}$ ID (e.g. uncoated copper)	<ul style="list-style-type: none"> • Low cost • Robust 	<ul style="list-style-type: none"> • Handling of micron wires can be difficult and size of void needs to be calibrated and represent undefined path • Holes can close up over time depending on material relaxation • No direct measurement of hole size 	<ul style="list-style-type: none"> • Reproducible leak size with defined capping parameter and wire size • Leak size only defined when measured relative to physical phenomenon • Need to consider copper wire diameter and elastomer behavior for consistency • Actual size depends on many parameters

“Container Closure Integrity Testing – Practical Aspects and Approaches in the Pharmaceutical Industry” PDA J. Pharma. Sci. Technol. 2017 Mar-Apr;71(2):147-162

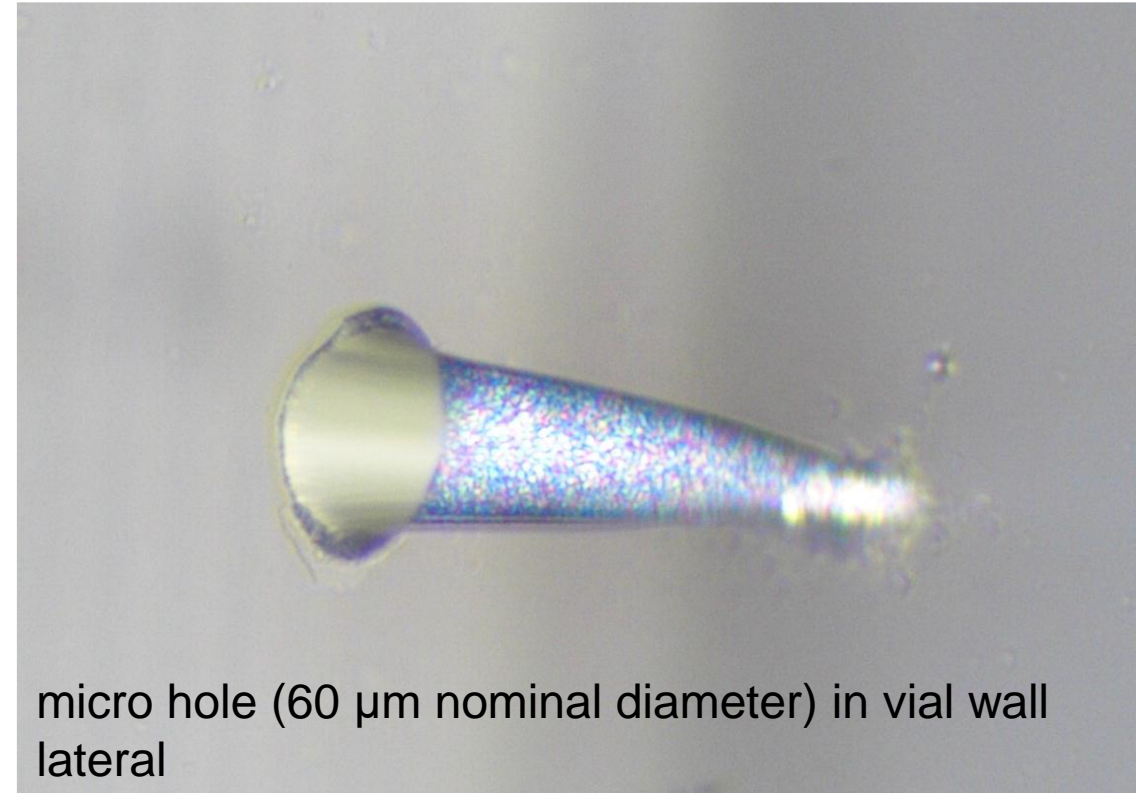
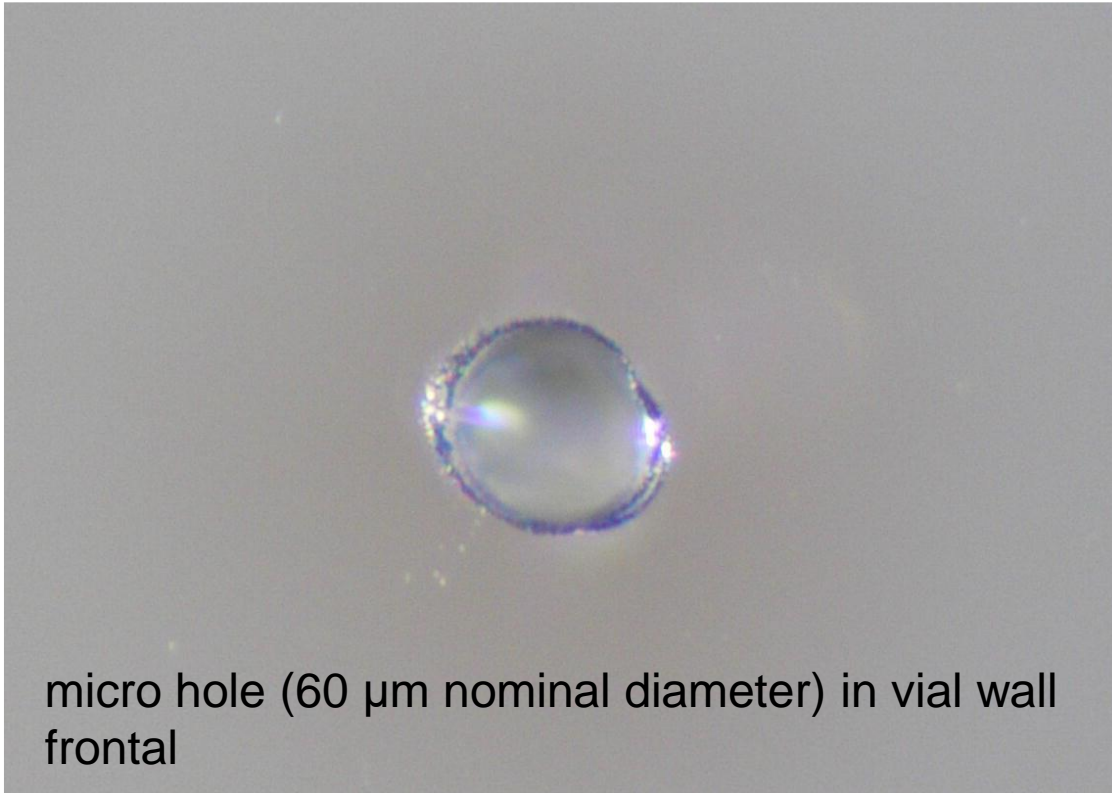
Common Hole Locations in Glass Vials



Common Hole Locations in Syringes



Micro hole leak: light microscope images of laser drilled



Capillary & Microfibers



Capillary with epoxy in sidewall



Copper wire between stopper and vial

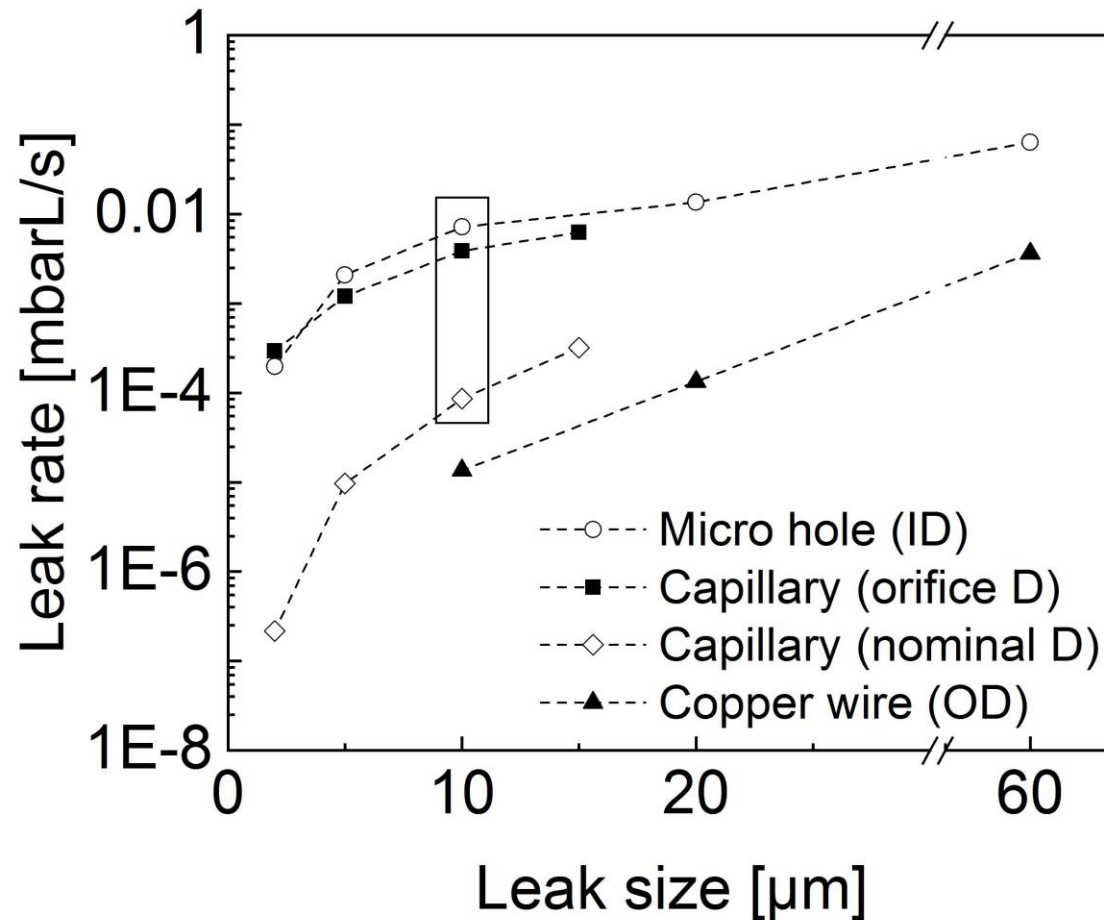
Percentage of detected leaks (n=10) for CCIT Methods



Artificial Leak	Leak Size	He Leak	Vacuum Decay	HSA	Dye Ingress
Negative Control		0%	0%	0%	0%
Micro hole (ID)	60 µm	100%	100%	100%	100%
	20 µm	100%	100%	100%	100%
	10 µm	100%	100%	100%	100%
	5 µm	100%	100%	100%	60%
	2 µm	100%	0%	0%	0%
Capillary (orifice diameter)	15 µm	100%	100%	100%	90%
	10 µm	100%	100%	100%	100%
	5 µm	100%	100%	100%	50
	2 µm	100%	10%	100%	0%
Capillary (nominal diameter)	15 µm	100%	20%	100%	0%
	10 µm	100%	0%	0%	0%
	5 µm	100%	0%	0%	0%
	2 µm	100%	0%	0%	0%
Copper wire (OD)	60 µm	100%	100%	100%	100%
	20 µm	100%	20%	0%	0%
	10 µm	100%	40%	0%	0%

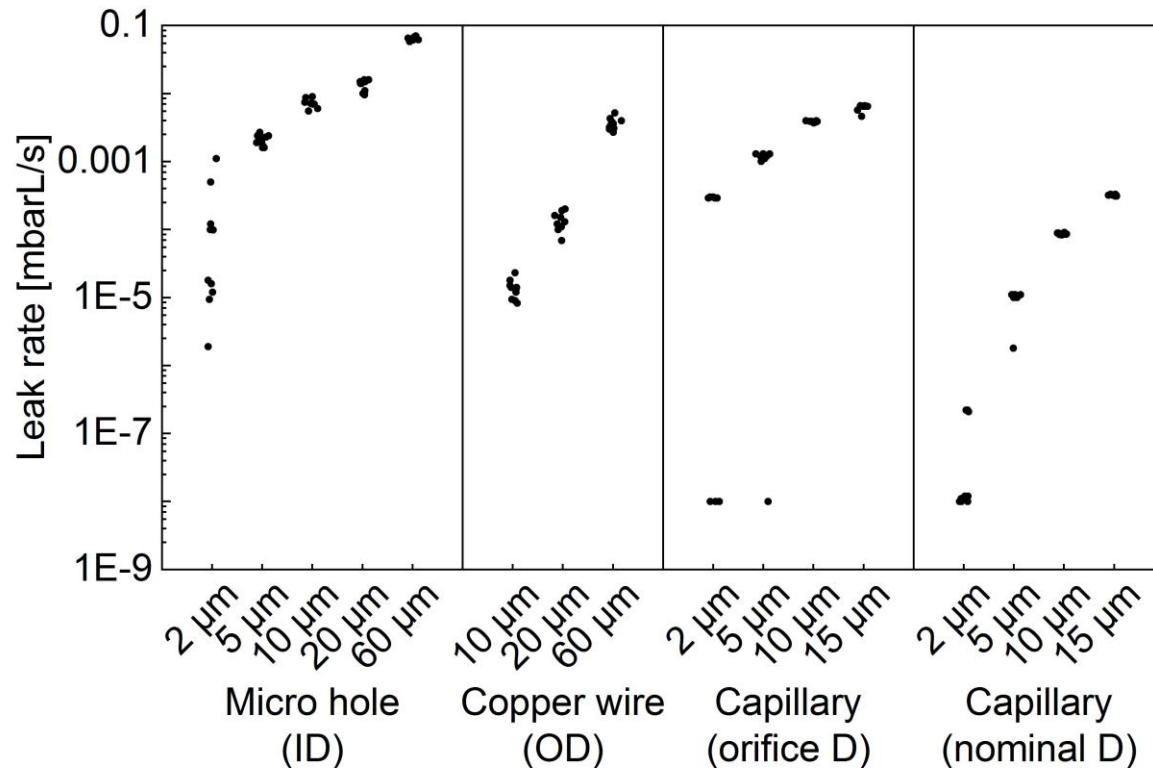
COPYRIGHT © PDA 2018

He Leak Rates for Artificial Leaks



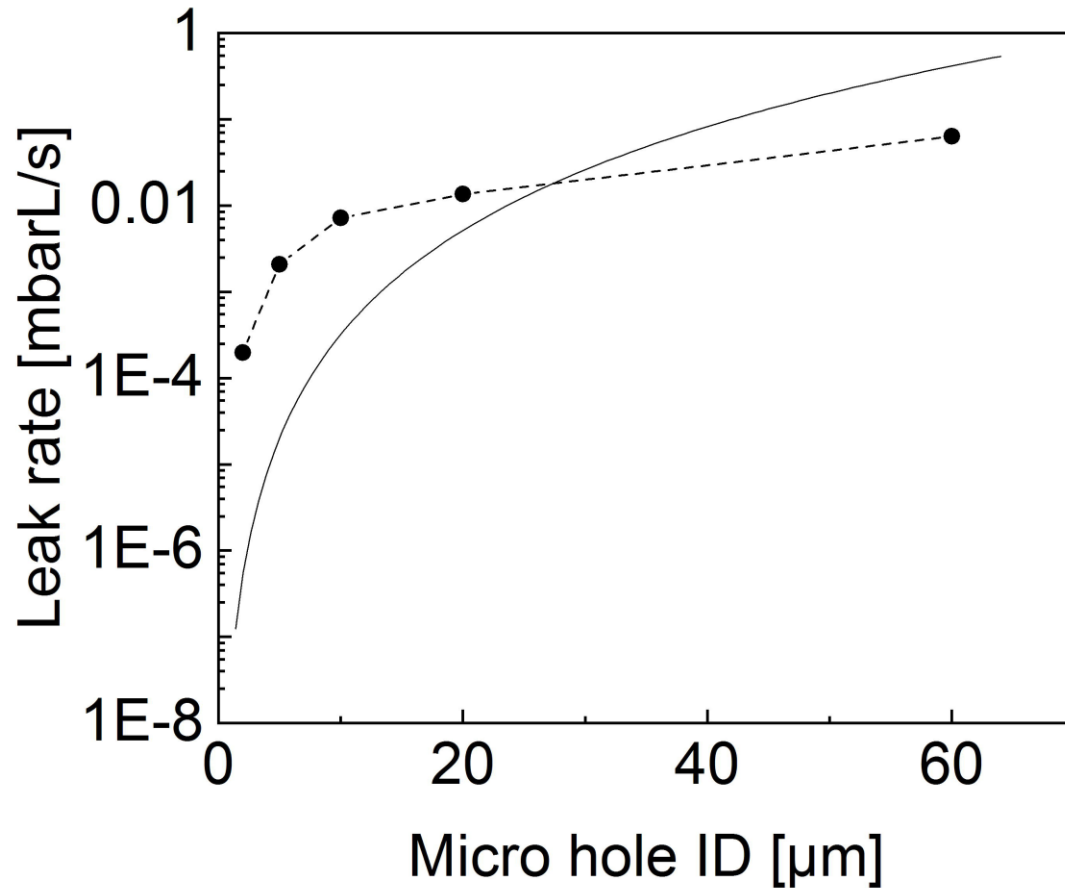
- He leak rates increase with larger leak sizes
- Leak types show specific leak rates according to leak geometries
- 3 leak types at 10 µm significant differences in He flow rates
- Theoretical leak rates from equation micro hole = capillary leak (orifice diameter) > capillary leaks (nominal diameter) > copper wire
- Strong dependence of glass flow rate on leak path length

Variability of Leak Rates of Artificial Leaks



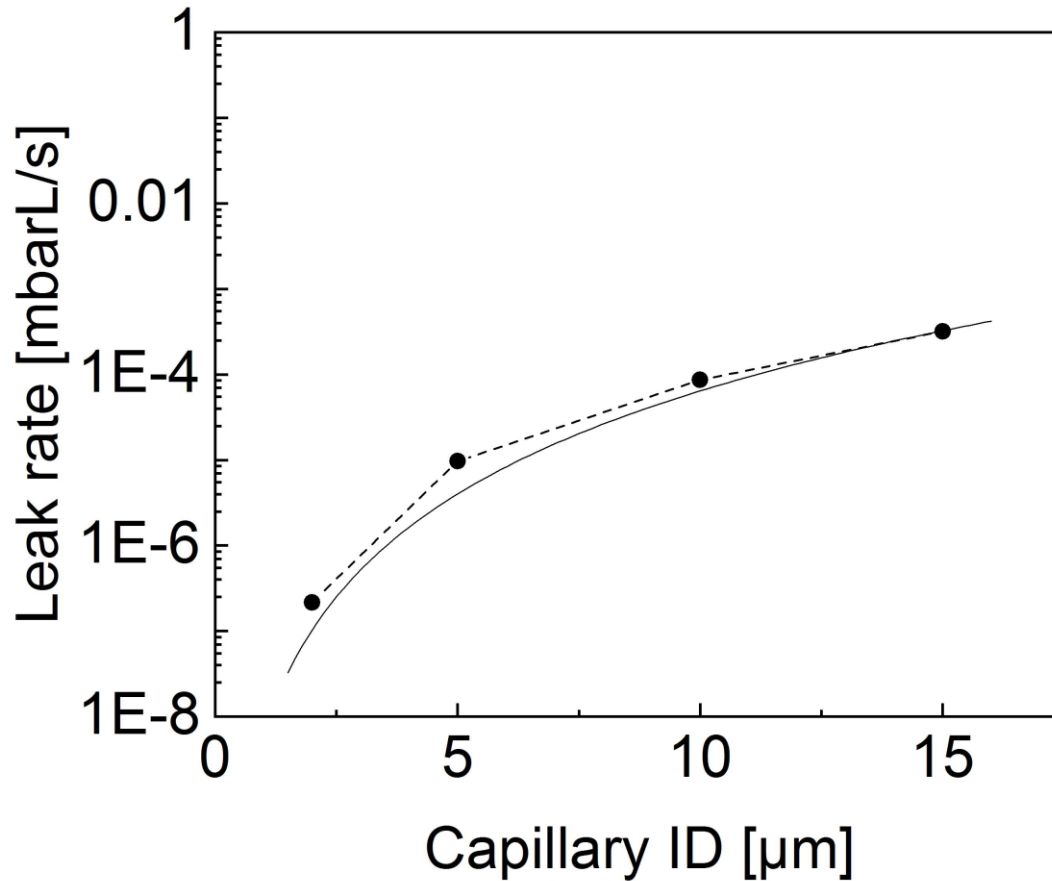
- Variability increased for smaller leaks
- Artificial leaks can have significant variability in actual leak size and deviation from target
- Micro holes highest variability, especially at smallest diameter (complex and irregular shapes of micro hole channels contributes)
- Capillary leaks are consistent channels with know ID, but are quite different than real-life leaks
- Capillary leaks of very small ID can become clogged or defective (see very low leak rates), capillary leaks must be prepared with care and handled with care
- Copper wire can have kinks in the wire, become entrapped in rubber stopper wrinkles, breakage of wire; path length may vary based on stopper, leak channel size cannot be defined

He Leak Rates with Micro Holes vs Theoretical



- Actual leak rates vs theoretical leak rates
- Small micro holes were much larger than expected and declared by supplier – defect could increase in size during shipping or handling

He Leak Rates with Capillaries vs Theoretical



- Actual leak rates vs theoretical leak rates
- Capillaries with nominal diameters show good correlation to estimated theoretical leak rate at all sizes

Comparing Capillary Leaks with Nominal Diameter and Orifice Diameter

- Orifice diameter prepared by adjusting length and ID of capillary according to calculated leak rate
- Nominal diameter prepared with consistent length and varying ID of capillary
- Orifice sizes higher He leak rates for all sizes compared to nominal diameter
- Nominal diameter He leak rates were lower because of the negative proportional relation of the path length to the leak rate

Importance of capillary diameter and path length