## Artificial Leaks / Positive Controls







#### **Artificial Leaks**

- Artificial leaks are required in order to assess CCIT method capability to detect a leak
- Artificial leaks are require din 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



2



Leak Type	Advantages	Disadvantages	Experiences
Mirco-pipettes, ≥0.1 µm ID (e.g. glass)	Easy sample preparation	<ul> <li>Fragile &amp; broken tips may not be detected</li> <li>Difficult to determine hole size</li> <li>Difficult to handle</li> </ul>	<ul> <li>Too fragile for routine use</li> <li>High risk of false sensitivity</li> <li>Need complete seal around micropipette</li> <li>Silicone oil can clog</li> <li>Pinhole type defect</li> <li>Material matches primary container if glass is used</li> </ul>
Laser-drilled holes, ≥0.5 µm ID	<ul> <li>Wide range of sizes</li> <li>Better resembles natural defects (cracks in glass; pinholes in polymer)</li> <li>Newer techniques allow for defined holes; fewer cracks</li> </ul>	<ul> <li>Cost</li> <li>Size of laser-drilled void needs to be calibrated and represents defined path</li> <li>Small hole can clog (silicone, viscous liq)</li> <li>Holes can increase in size (temp changes, tension)</li> <li>Variability in sizes depending on material/ wall thickness</li> <li>Irregular shapes</li> <li>Cannot be prepared on product</li> </ul>	<ul> <li>Risk of alteration post manufacture/calibration</li> <li>Specialized external supplier</li> <li>Many material can be drilled</li> <li>Closer to real world defects</li> <li>May reuse positive controls</li> <li>Dirt or particulates could impact quality of holes</li> </ul>

"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, ≥0.2 µm ID (e.g. fused silica)	<ul> <li>Robust</li> <li>Easy preparation at testing location</li> <li>Possible to prepare controls in specific packaging format and for multiple products</li> <li>Prepared in flexible way (e.g. may contact liq and headspace)</li> </ul>	<ul> <li>Length of microtube defects is usually longer than real world defects</li> <li>Typically nominal diameters &gt; 2µm available &amp; uncertainty of actual diameter</li> <li>Capillary diameter and hold diameter not comparable with regard to flow rate</li> <li>Glue can create blockage</li> </ul>	<ul> <li>Robust, wide size range &amp; different materials available</li> <li>Leakage rates can be fine-tuned through length of capillaries; not only using IDs</li> <li>Consistent dimensions/leaks</li> <li>Defined dimensions mean don't have to calibrate each lead</li> </ul>
Micron wires, ≥10 µm ID (e.g. uncoated copper)	• Low cost • Robust	<ul> <li>Handling of micron wires can be difficult and size of void needs to be calibrated and represent undefined path</li> <li>Holes can close up over time depending on material relaxation</li> <li>No direct measurement of hole size</li> </ul>	<ul> <li>Reproducible leak size with defined capping parameter and wire size</li> <li>Leak size only defined when measured relative to physical phenomenon</li> <li>Need to consider copper wire diameter and elastomer behavior for consistency</li> <li>Actual size depends on many parameters</li> </ul>

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#### **Common Hole Locations in Glass Vials**







#### **Common Hole Locations in Syringes**







# Micro hole leak: light microscope images of laser drilled



micro hole (60 µm nominal diameter) in vial wall frontal





Sarah S Peláez, Hanns-Christian Mahler, Christoph Herdlitschka, et al. PDA Journal of Pharmaceutical Science and Technology 2019. "Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies."



#### Capillary & Microfibers





Sarah S Peláez, Hanns-Christian Mahler, Christoph Herdlitschka, et al. PDA Journal of Pharmaceutical Science and Technology 2019. "Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies."



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

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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	15 µm	100%	100%	100%	90%
diamer)	10 µm	100%	100%	100%	100%
	5 µm	100%	100%	100%	50
	2 µm	100%	10%	100%	0%
Capillary	15 µm	100%	20%	100%	0%
(nominal diameter)	10 µm	100%	0%	0%	0%
	5 µm	100%	0%	0%	0%
	2 µm	100%	0%	0%	0%
Copper wire	60 µm	100%	100%	100%	100%
(OD)	20 µm	100%	20%	0%	0%
COPYRIGHT © PDA 2018	10 µm	100%	40%	0%	0%

## 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 mirco 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



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# 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 rats were lower because of the negative proportional relation of the path length to the leak rate

#### Importance of capillary diameter and path length

