Considerations	Best Case Practical Detection Limit	Detection	Destructive	Qualitative (Pass/fail) or Quantitative (measuring leak size)	Typical Applications — Container/ Closure (C/C) development, qualification	Typical Applications — Routine QC testing (e.g. lot releae, stability)	Typical Applications — 100% in-line testing potentially feasible	Major Advantages	Major Limitations	Key Considerations
Headspace	0.01 µm low LOD	Deterministic	Nondestructive	Both Qualilative and Quantitative (using diffusion model cailbration)	Y (MALL)	Y	Widely used	Sensitive (can be used to demonstrate conformance to MALL, given adaquate time); Non-destructive, same samples can be tesed at various stability time points; on-line 100% testing; Ease of use; fast analysis for routine testing; compatable with transparent glass or plastic. Capable of detecting temporary leaks due to its "cummulative" ingress detection over a long period of time; Can measure CO_2, O_2 and vacuum as indicator gases (different instruments needed); A perfect fit for oxygen sensitive products packaged in modified atmosphere (e.g. nitrogen).	Need at least 3 mm of headspace to perform test; liquid can permeate into headspace - need to understand transfer rate from liquid into headspace; transparent containers only; cannot indicate leak location; May require long "hold tiime" to achieve sensitivity.	Fixture design may be needed	MALL - need long periods of time to achieve the lowest detection limit.
Vacuum/ Pressure Decay	2-5 µm low LOD; Gross leak detection needs to be defined	Deterministic	Nondestructive	Qualitative, quantitative feasible	Y (not MALL)	Y	Feasible	Potentially applicable to injection devices; non-destructive; ease of use; testing speed (<1min/sample); dry/liquid product,	Proteinaceous products may interfere defect detection; contamination concerns due to DP leakage during testing; surface moisture/condensation can cause false positives - need to dry before test; cannot measure to MALL level (i.e. 0.2-0.3 micron levels);	Ensure proper fixture design to prevent plunger movement and deformation	Sample surface and vacuum chamber preparation are critical
Mass Extraction	1 µm low LOD; Gross leak detection needs to be defined	Deterministic	Nondestructive	Quantitative	Y (not MALL)	Y	Feasible	Potentially applicable to injection devices; vials, syringes, flexible packaging; 1 setup can be used for multiple volumes - change parts, quantitates leak rate against leak standard; easy to validate, high sensitivity; direct measurement of leak flow rates; Non-destructive: 100% capable	Proteinaceous products and silicone oil may interfere ("clog") defect detection; contamination concerns for DP leakage during testing; no ID of gas coming out; cannot ID location of leak; container needs to be dry; Sample chamber needs to be clean and free of externally "entrapped" air (free of volatile specieis, condensation) prior to testing, requires headspace or volatile liquid; Test usually performed at high level vacuum (higher than typical vacuum level seen during transportation);	Ensure proper fixture design to prevent plunger movement and deformation	Sample surface and vacuum chamber preparation are critical
High Voltage Leak Detection	1-5 µm	Deterministic	Nondestructive (note ozone impact on drug product should be considered for 100% testing)	Qualitative, quantitative feasible	Y (not MALL)	Y	Widely used	Testing under normal atmospheric pressure; Applicable to high-concentration proteinaceous products; Fast; In-line 100% testing used for decades on ampules etc.; Non-contact between electroded and C/C and less contaimination concern; can idicate leak location	Requires conductive fills; headspace areas need to be "wet" bu sample handling , non porous/non conductive packages only · Not applicable to auto-injector/pen devices; No Lyo products; Only applicable to non-porous packaging; flow under caps for vials and prefilled syringes · May cause drug product degradation due to ozone, flammable products are a risk · Signal not directly correlated to leak size	Understanding of drug product (conductivity) and packaging materials (conductivity, capacitance etc) is important; Syringe barrel area covered by needle shield may not assessable
Helium Leak Detection	<0.1-2 µm; gross leak detection may need to be determined	Deterministic	Nondestructive	Both Qualilative and Quantitative	Y (MALL)	Y (consider helium permeation ect prior to use in stability testing)	Feasible	Highly sensitive; specific - not interfered by other gases; applicable to empty containers; can add a sniffer probe to locate leak, can tell if approaching MALL, reproducible; can isolate and identify leak location; Directly measure leak flow rates	Requires helium-containing headspace for drug product-filled syringes; permeation can cause challenges with false positives; May miss large leak if helium escape through large defectds - need to ID gross leaks before using HeLD; used for achieving MALL of 0.2 microns, non porous packages only; difficult to use as a online 100% detection. Sample prep can be complex (helium charging etc).	Ensure sample surfaces are free if adsorbed helium prior to testing to avoid false detection; atmospheric helium levels can cause interference (sniffer mode). Intent of test - to id large leaks or submicro leaks (risk based approach); Tranferabulity and applicability in mfg settings
Dye Ingress	20-50 µm	Probabilistic	Destructive	Qualitative only	Y	Y	No	Widely used for decades · Industry and regulatory familiarity · "Last resort," when all else fails	Less sensitive · Detection is probabilistic · Destructive	Ensure that a true failure can be detected (e.g., dye in syringe, liquid in ribs)
Microbial Ingress	20-50 µm	Probabilistic	Destructive	Qualitative only	Y	No (Sealing process validation)	No	Widely used for decades · Industry and regulatory familiarity · "Last resort" when all else fails	Less sensitive · Detection is probabilistic · Destructive · Not applicable to drug product filled syringes	Cannot assure the absence of pathogens
Optical Emission Spectroscopy	0.7 µm using micropipette on glass vial	Deterministic; uses a multigas sensor (N_2, H_2O, CO_2, Air)	Non-Destructive	Quantitative	Y	No	No	High sensitivity and through-put · No sample Preparation · Air and Water leaks can be detected simultaneously	Non-porous materials · Not recognized by USP 1207; not peer reviewed technique	Material in contact with vacuum (outgasing); available headspace