Considerations	Best Case Practical Detection Limit	Detection	Destructive	Qualitative (Pass/fail) or Quantitative (measuring leak size)	Typical Applications			Major Advantages			Major Limitations				Key Considerations	
					Container/ Closure (C/C) development, qualification	Routine QC testing (e.g. lot releae, stability)	100% in-line testing potentially feasible									
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); Tranferability 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	