

the curve demonstrates a noticeable decrease; in other words, the second derivative reached a maximum value.

Published research by Morton et al. first described RSF measurement using a universal tester and demonstrated the method's usefulness. RSF measurements were proven sensitive to differences in elastomeric formulation, elastomeric stopper manufacturing lots, time post capping, and exposure to terminal steam sterilization (30,31). Lower RSF values correlated to increased package leakage rate measured by a pressure decay method, a bubble test, a liquid tracer test, and a microbial challenge test (8).

Later, a team of researchers lead by Ludwig optimized the RSF method by modifying the metal cap anvil placed on top of a vial (32,33). Rounding the top of the metal cap anvil helped to make a more uniform compression of slightly imperfect vials and making the cap fit more tightly helped improve centering of the cap anvil onto the vial.

As previously mentioned, RSF itself is not a leak test method. RSF alone is insufficient for parenteral package integrity assurance. A package capped at optimum RSF may leak if the vial or stopper is defective. Conversely, research has shown that a vial package assembled using defect-free components may leak if poorly capped, as measured by RSF (24). RSF measurements are important when optimizing and verifying capping machine setup. No other method, including visual inspection or manually twisting the capped vial to determine "tightness" has proven reliable.

Vacuum Decay Leak Tests

Vacuum decay is a whole package, nondestructive leak test method that has grown in popularity over the past 20 years. Today's test systems range from small benchtop laboratory instruments to production scale 100% fully automated on-line machines. In a typical test cycle, the test package is placed in a test chamber, the chamber is closed, and vacuum is rapidly drawn to a target pressure level within an allotted time segment. After establishing vacuum, the test system is isolated from the vacuum source, and any subsequent pressure rise (vacuum decay) inside the test chamber is monitored. Pressure rise above baseline, or background noise level, signifies package headspace gas leakage, and/or vaporization of product liquid plugging leak path(s). Total test cycle time is normally less than 30 seconds, but may vary with the test system, the product-package tested, and the desired sensitivity level.

The test equipment, package test chamber, and testing cycle are unique to each product-package system, and are specified based on the package's contents (liquid or solid, with significant or little gas headspace), package morphology (flexible or rigid, porous or nonporous), and package size. Uniquely designed test chambers snugly enclose the test package, minimizing test chamber deadspace for maximum test sensitivity. Added features may be required to limit package movement or expansion during the test (e.g., prefilled syringes, flexible bags, or pouches), or to mask gas flow through porous barrier materials (e.g., paper or Tyvek®) (34). Test systems are configured either to detect leaks in packages filled with liquids, or to detect leak paths in packages containing gases and/or solids. Leak paths that risk liquid clogging, or "liquid leaks," require higher vacuum test conditions below the liquid's vaporization pressure, so that vaporized liquid yields a measurable rise in pressure. On the other hand, "gas leaks" are detectable at less severe vacuum settings.

Vacuum decay leak tester designs vary among instrument manufacturers. While most models rely on a single 1000 Torr gauge or absolute transducer, some instruments use a dual transducer system with either a 1000 Torr gauge or absolute transducer coupled with a more sensitive, higher resolution 10 Torr gauge transducer. One manufacturer that relies on the single-gauge transducer approach also incorporates special software that continually readjusts the no-leak baseline to account for atmospheric pressure changes and no-leak noise variations that can affect test sensitivity. Another vendor is able to eliminate atmospheric pressure variation concerns and the need for calculated baseline adjustments by utilizing an absolute pressure transducer as part of their dual transducer test system (35).

Test method development and instrument functionality checks often utilize either a calibrated fixed orifice leak or a calibrated airflow meter for artificially introducing leaks into the test chamber containing a negative control no-leak package. Airflow meters certified by the NIST or other recognized certification bodies are recommended for such purposes. The smallest