negative controls in a randomly mixed, blinded test sample population. A multisite study led by Wolf demonstrated how differences in inspector capabilities and inspection environments play a significant role in interpreting dye ingress test results (20).

Numerous published leak test studies incorporate dye or liquid tracer test methods (8,11,13). U.S. compendia (21), EU compendia (22), and ISO international standards (12) all specify methylene blue dye ingress tests for demonstrating punctured closure reseal properties. But before using such closure reseal methods for whole package integrity testing, test parameters should be optimized and the methods validated using known positive and negative control packages. The importance of this was demonstrated in the study by Wolf et al., in which 1-mL water-filled syringes with laser-drilled defects in the barrel wall ranging in nominal diameter from 5 to 15 μm were leak tested according to the closure resealability dye ingress tests described in the U.S. and EU compendia and in ISO standards. None of these standard test methods permitted accurate identification of all defective syringes (20).

Electrical Conductivity Tests

The electrical conductivity leak test, also termed high voltage leak detection (HVLD), attempts to pass a high-frequency high voltage electrical current from an electrode positioned near the test package to a ground wire positioned at the far end of the package opposite the probe. Test packages made of plastic, glass, or elastomer are relatively resistant to current (i.e., insulating or nonconductive), and so allow minimal current to pass from electrode to ground—approximately 1 to 4 volts. If, however, a package leak is present near the electrode, with liquid product relatively conductive at or near the leak, a spike in measured current passing through the package will occur.

Möll et al. described test method development and validation of an electrical conductivity test used for gel-filled low-density polyethylene ampoules (23). Positive controls consisted of ampoules with laser-drilled holes positioned at the most likely zones for leaks to occur: the sealing zone at the ampoule bottom, and the top tear-off area. The voltage setting and the sensitivity or "gain" setting were the two parameters optimized to establish a window of operation that finds all defective ampoules and rejects few, if any, good ampoules. Replicate testing of a randomized population of negative and positive control test samples took place over three days. On each day of operation, the HVLD test successfully "failed" all 210 positive control ampoules (150: 5–10 μm; 60: 10–20 μm) and "passed" 3830 negative controls. A dye ingress test confirmed the presence of defects in two of three so-called negative controls consistently rejected by HVLD. Therefore, the electrical conductivity test correctly identified all defective units and falsely rejected only one negative control sample.

Recent studies have shown that HVLD is able to detect loosely capped stoppered vial packages, despite the absence of package component defects (24). The same work showed the method's ability to defects clogged with proteinaceous active compound, defects not detected by the vacuum decay method. In addition, multiple exposures to HVLD tests had no deleterious effect on three proteinaceous active substances, although additional testing would be required to fully qualify the method's product compatibility.

For obvious reasons, electrical conductivity is not appropriate for testing flammable liquid products. In addition, only leak paths near detectors are identifiable; therefore, either package surfaces are checked using multiple detectors or only the areas of greatest risk for leakage are monitored. Package rotation during testing may be required in order to capture defects around a package's circumference. Test method validation for a given product-package requires demonstration of the test's ability to detect leaks at all likely package locations.

Given HVLD's ability to rapidly and cleanly test a wide variety of product-package systems for the smallest leaks, this method's use is expected to expand in the future.

Frequency Modulation Spectroscopy

Frequency modulated spectroscopy (FMS) is a rapid, nondestructive analytical method suitable for monitoring oxygen and water vapor concentrations as well as evacuated pressure levels in the headspace of sterile product containers. Over the last 10 years, the technology has found commercial application in the pharmaceutical industry for leak detection (25), moisture monitoring (26), and oxygen monitoring (27). Systems for rapid nondestructive headspace analysis