airflow rate that triggers a rise in pressure above background noise level is the limit of detection for the leak test.

However, use of calibrated airflow standards alone is not sufficient for complete test method development and validation. Positive control, with-leak packages should be used as well, in order to best understand how test chamber pressure rise compares for various sized leak paths positioned in various package locations. For example, a gross leak in a package with minimal gas headspace volume may not be detected if the time allotted for initial vacuum is so long that all headspace gas is evacuated prior to the start of the pressure rise test phase. In another example, a plastic bottle with a pinhole-size leak in the induction seal, beneath the torqued screw thread cap may require additional time to draw out trapped air in the cap's threads, before leakage through the induction seal hole is observed. Further, leaks simulated using a calibrated flowmeter only represent gaseous leakage and not leakage from liquid-plugged leak paths. Generally, liquids clogging leaks quickly volatilize once test pressure falls below the liquid's vaporization pressure, triggering a rapid rise in test system pressure. Pressure rise quickly stops and perhaps fluctuates once the vaporized liquid's saturation partial pressure is reached. This difference in leak behavior between so-called liquid versus gas leaks often requires different testing parameters. Additionally, test system cleaning procedures should be in place in anticipation of test equipment contamination from liquid-filled leaking containers. Negative control, no-leak packages may be solid material, package-shaped models, but at some point, larger test populations of actual, filled, no-leak packages are important to ensure the validated baseline represents all possible package-to-package variations.

In the late 1990s, the functionality of Wilco AG vacuum decay leak test systems was explored by Kirsch, Morton, and a team of researchers from Wilco in two published research studies. For both studies, test samples consisted of glass vials with micropipettes affixed into the glass vials to simulate leaks. Test package leakage was quantified using helium mass spectrometry, a leak test method previously compared with liquid-borne microbial challenge tests. In the first study, air-filled vials were vacuum decay leak tested (15). The second study evaluated vials filled with various solvents that plugged the leak paths using an "liquid-filled container (LFC)" pressure rise or vacuum decay approach. This concept required the test pressure to be substantially lower than the vapor pressure of the packaged liquid (16). LFC method test results indicated potentially greater sensitivity when testing liquid-filled vials.

ASTM F2338-09 standard test method for nondestructive detection of leaks in packages by vacuum decay method (36) is a recognized consensus standard by the United States FDA, Center for Devices and Radiological Health (CDRH), effective March 31, 2006 (37). According to the FDA Consensus Standard Recognition Notice, devices that are affected include any devices that are sterilized and packaged. Packages that may be nondestructively tested by this method include: rigid and semirigid nonlidded trays; trays or cups sealed with porous barrier lidding materials; rigid, nonporous packages; and flexible, nonporous packages.

The ASTM method includes precision and bias (P&B) statements for various types of packages based on round robin studies performed at multiple test sites with multiple instruments. P&B studies have looked at porous lidded plastic trays, unlidded trays, and induction-sealed plastic bottles with screw caps. The most recent P&B studies used glass prefilled syringes; a publication fully describing this work appeared in 2009 (35). Test packages included empty syringes, simulating gas leaks; and water-filled syringes, simulating leaks plugged with liquid (liquid leaks). Laser-drilled holes in the syringes' glass barrel walls ranging from 5 to 15 μm in nominal diameter served as positive control leaks. The leak testers used incorporated a 1000 Torr absolute transducer coupled with a 10 Torr differential transducer, manufactured by Packaging Technologies & Inspection, LLC of Tuckahoe, New York. Two different test cycles were explored; one with a target vacuum of 250 mbar absolute for testing gas leaks only, and another with a target vacuum of about 1 mbar absolute for testing both gas and liquid leaks. P&B study results showed the leak tests reliably identified holes as small as 5 μm in both air-filled and water-filled syringes.

More recent research described in a public forum indicates that vacuum decay is at times limited in its ability to detect leaks in packages containing proteinaceous liquid products. Proteinaceous active in an aqueous formulation irreversibly clogged a large percentage of glass vial laser-drilled holes making their detection by vacuum decay impossible (24). This