

defects to represent the full range of anticipated leak sizes. If the primary leak test method fails to find the full range of package types and sizes of concern, then a second method may prove valuable. For example, high voltage leak detection may prove successful for 100% leak detection of a liquid product contained in a flexible pouch. However, larger gaps in the seal causing package collapse and liquid loss may be missed by this leak test system, making it important to screen for such larger leaks via visual inspection, weight checks, or some other means. Ironically, while the pharmaceutical industry has focused on finding the smallest package defects with better technologies, product recalls triggered by gross package integrity failures continue to occur.

### **PACKAGE INTEGRITY TEST METHODS**

Many leak test methods exist that are applicable to pharmaceutical package systems. The goal of this chapter is not to describe all such methods. Instead, a review is offered of a few of the most commonly used methods and those proven to be most valuable to the pharmaceutical industry. These methods are presented in alphabetical order.

#### **Bubble Tests**

A bubble test is performed by immersing the package in water, drawing a vacuum, and observing for bubbles. Alternatively, a pressure source can be inserted into the package, allowing package pressurization during immersion. Immersion fluid surfactants improve method sensitivity. Bubble tests are quick and useful for leak presence and location confirmation in a laboratory setting. Smallest leaks may be missed if leaking gas dissolution rate in the immersion fluid is faster than bubble formation rate. Trapped gas on package seal surfaces may be confused for leaks. A common mistake when testing flexible packages is to fail to restrict test package volume, allowing package ballooning or expansion during vacuum exposure. Expansion will cause a drop in internal package pressure, eliminating the differential pressure necessary for bubbling to occur. A bubble test is a very useful forensic testing tool, but because it is destructive and test results are variable, it should not be used to access finished product quality.

#### **Dye or Liquid Tracer Tests**

A liquid tracer leak test consists of immersing test packages in a solution of either dye or other chemical tracer, then allowing time for liquid to migrate through any leaks present while pressure and/or vacuum are applied. After the liquid challenge, test packages' contents are checked for liquid leakage either visually or by using an appropriate analytical method. Liquid tracer leak tests are relatively inexpensive, simple to perform and conceptually easy to understand. However, the test is destructive to the package, and results may vary considerably. Dye or liquid tracer tests are inappropriate for testing product that may enter the market or clinic due to the risk of product contamination incurred by the method.

Test method parameters that promote greater liquid tracer test sensitivity include longer immersion times, increased pressure and vacuum conditions, smaller volumes inside the test package, and lower surface tension challenge liquids. Debris, airlocks, and event clogs of proteinaceous product may easily hamper leak path liquid migration. Restraining package part movement (e.g., prefilled syringes), or package expansion (e.g., flexible pouches) during vacuum exposure helps keep package internal pressure constant, thus ensuring consistent leakage driving forces.

Method development requires verification of dye or tracer compatibility with the package and its contents. Methylene blue is commonly used, but other chemicals specifically chosen for product compatibility are acceptable (19). Dyes may quickly fade or adsorb onto package surfaces shortly after leak testing; therefore, time gaps between testing and inspection or analysis should be limited and specified. Any dye or tracer detection method also requires validation. Human inspection is considered less reliable than analytical detection techniques. For the best visual inspection results, use qualified inspectors trained to follow defined inspection procedures in well-lit, controlled inspection environments. Inspection procedures should dictate lighting intensity and color, inspection angle, background color(s), background luster, inspection pacing, and any comparator negative control package(s) used. Inspector qualification protocols should entail accurate segregation of packages containing trace amounts of dye from