methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals."

The 2004 U.S. FDA Sterile Drug Products Aseptic Processing GMPs delineate similar standards to those in the European GMPs (5). Referring to inspection of container–closure systems, "Any damaged or defective units should be detected, and removed, during inspection of the final sealed product. Safeguards should be implemented to strictly preclude shipment of product that may lack container-closure integrity and lead to nonsterility. Equipment suitability problems or incoming container or closure deficiencies can cause loss of container-closure system integrity. For example, failure to detect vials fractured by faulty machinery as well as by mishandling of bulk finished stock has led to drug recalls. If damage that is not readily detected leads to loss of container-closure integrity, improved procedures should be rapidly implemented to prevent and detect such defects." Appendix 2 entitled Blow-Fill-Seal Technology states the following: "Container closure defects can be a major problem in control of a BFS operation. It is critical that the operation be designed and set-up to uniformly manufacture integral units. As a final measure, the inspection of each unit of a batch should include a reliable, sensitive, final product examination that is capable of identifying defective units (e.g., leakers). Significant defects due to heat or mechanical problems, such as wall thickness, container or closure interface deficiencies, poorly formed closures, or other deviations should be investigated in accordance with §§ 211.100 and 211.192."

PDA Technical Report No. 27

The Parenteral Drug Association (PDA) published a technical resource to offer clarification about selection of appropriate container–closure integrity test methods for different types of packaging (6). This report summarizes package leakage concepts and critical leak specifications and discusses the need to consider package integrity for the life of the product beginning in early product development. Eighteen different integrity tests are described and referenced. These are linked to a decision tree to help the reader in selecting the most appropriate methods. While the PDA Technical Report No. 27 is not an official regulatory document, for years it provided a valuable resource when first selecting package integrity tests. However, given the rapid developments in leak testing technologies during the last decade, the reader is advised to also consult more current sources for newer developments in package integrity testing.

LEAKAGE UNITS OF MEASURE

Leakage is mathematically defined as the rate at which a unit of gas mass (or volume) flows into or out of a leak path under specific conditions of temperature and pressure. The units of measure commonly used in many literature references to specify leakage rate are standard cubic centimeters per second (std cm^3/sec or std cc/sec). According to the international metric system of units (SI nomenclature) leakage is measured in pascal cubic meters per second (Pa $\cdot$ m^3/sec). In both expressions, units of gas mass (std cc and Pa $\cdot$ m^3) indicate the quantity of gas (air) contained in a unit of volume at sea level atmospheric pressure (101 kPa). The std cc/sec is the more common unit of measure. To convert to std cc/sec from Pa $\cdot$ m^3/sec, the SI units should be multiplied by a factor of 9.87, or approximately 10. When expressing leakage volumetrically, rather than in mass flow units, test pressure and temperature conditions should be specified.

CRITICAL LEAK RATE AND SIZE

All parenteral product packaging must maintain product sterility by preventing the ingress of microorganisms. Therefore, the "critical leak rate" is generally understood to mean that leak rate, corresponding to a leak path that will permit microbial ingress. Pharmaceutical, medical device, and food packaging scientists have worked for many years to define this "critical leak rate" and its corresponding "critical leak size." Research results and conclusions derived from these studies vary widely. Differences seem to be colored by the perceived microbial ingress risk to product quality. For example, medical device experts who rely on nonporous as well as porous barrier material packaging are generally concerned with air-borne, rather than liquid-borne microbial challenges. Food packaging scientists are concerned with liquid-borne microbial ingress; however, food products often have a relatively short shelf life, may include antimicrobial preservatives, and are always ingested rather than injected, making the tiniest integrity breaches of a few microns or less of minor concern. On the other hand, pharmaceutical