⟨1207⟩ PACKAGE INTEGRITY EVALUATION—STERILE PRODUCTS

1. INTRODUCTION

This chapter provides guidance on the integrity assurance of nonporous packages intended for sterile pharmaceutical products. Background instruction is provided on the topics of leaks, leakage rate, and package sealing/closure mechanisms. Explanation is given as to how packages that conform to specified leakage limits help to ensure the contained product meets and maintains sterility and relevant physicochemical specifications. The integration of package integrity assurance as a key component of the entire product life cycle is stressed. Guidance in the selection, validation, and use of leak test methodologies as well as package seal quality tests is included. Detailed recommendations are presented in three subchapters listed below:

- *Package Integrity Testing in the Product Life Cycle—Test Method Selection and Validation* ⟨1207.1⟩
- *Package Integrity Leak Test Technologies* ⟨1207.2⟩
- *Package Seal Quality Test Technologies* ⟨1207.3⟩

At the end of this chapter, the *Glossary* section defines terms as they are used in the context of this set of four general information chapters.

The term product–package refers to the container–closure system plus the product contents. The container–closure system consists of the primary packaging components, those components that are or may be in intimate contact with the product, as well as secondary packaging components vital to ensuring correct package assembly, for example, the aluminum cap used to seal a stoppered vial package.

Suitable container–closure systems adequately store and protect the contained pharmaceutical product. Thus, sterile product–package integrity is the ability of a sterile product container–closure system to keep product contents in, while keeping detrimental environmental contaminants out. Specifically, leaks of concern for sterile product–packages include the following three categories described in *Table 1*. In other words, the leaks of concern for a given product–package are a function of the degree of package protection demanded by the product to ensure that all relevant product physicochemical and microbiological quality attributes are met through product expiry and use.

Table 1. Product Quality Risks Posed by Leaks of Concern

Leaks of Concern	Product Quality Risks Posed by Leaks
Capable of allowing entry of microorganisms	Failure of product sterility quality attribute
Capable of allowing escape of the product dosage form or allowing entry of external liquid or solid matter	Failure of relevant product physicochemical quality attributes
Capable of allowing change in gas headspace content. For example, loss of headspace inert gases (e.g., nitrogen), loss of headspace vacuum, and/or entry of gases (e.g., oxygen, water vapor, air).	Failure of relevant product physicochemical quality attributes and/or hindrance of product access by the end-user

Package integrity is synonymous with container–closure integrity; these terms are used interchangeably throughout this chapter. In the past, to say a sterile product–package has container–closure integrity commonly meant that the package either had passed or was capable of passing a microbiological challenge test. This guidance chapter defines the concept of container–closure integrity more broadly, encompassing the absence of all package leaks that risk product quality. By this definition, a package is considered to have integrity if it allows no leakage greater than the product–package maximum allowable leakage limit. In other words, the largest and smallest leaks of concern are absent.

Leakage differs from permeation. Leakage is the unintentional entry or escape of matter (solids, liquids, or gases) through a breach in a package wall or through a gap between package components. Leakage can also refer to the leaking matter itself. Leakage flow rate is a function of the absolute and/or partial pressure gradient of leaking matter that exists across the package barrier. In the context of this chapter, permeation is the passage of fluid (e.g., gas) into, through, and out of a nonporous package wall. Permeation, not leakage, occurs when only a small fraction of molecules is able to move through a barrier by way of any one hole. A nonporous package is able to permit permeation, but not the volumetric flow of air. Package permeation test methodologies fall outside of the chapter scope and are not described.

Package integrity tests are leak test methods. A leak test is a method that detects the presence of (and in some cases, the magnitude or location of) a package breach or gap.

Package seal quality tests are techniques used to characterize and monitor the quality and consistency of a package seal or closure system parameter, which can influence the package's ability to maintain integrity. An example is the peel force test widely used to test seal strength. Seal quality tests are not leak tests but can play a valuable role by monitoring a characteristic of the seal itself, the package materials, the package components, and/or the processes required to create the seal or closure mechanism.

Integrity test methods vary not only in their application and detection limit, but also in terms of detection range, precision, and specificity, for example. No one test is appropriate for all packages or for all leak testing applications. Selection criteria for package integrity test methods, as well as method comparison aids, are presented to guide the user in the selection process.

Leak tests, even many commonly recognized industry standard testing approaches, require optimization and validation for each product–package application. A science- and risk-based approach may allow some tests to be leveraged for broader application under certain circumstances. For example, small differences in product formulation or package design and materials may permit the use of one test for multiple product–packages. Package integrity verification plays an important role throughout the product life cycle, starting with product development and continuing through marketed product stability studies.

2. SCOPE

The package integrity leak tests and seal quality tests outlined in this chapter apply to the testing of both large and small volume container–closure systems for sterile pharmaceutical dosage forms. Such package systems include, but are not limited to, the following examples.

- Vials or bottles closed with elastomeric closures or screw-thread caps
- Form-fill-seal plastic or glass ampules
- Syringes or cartridges
- Flexible bags or pouches
- Packages for some drug/device combination products (e.g., packages cased inside autoinjectors)

Outside the chapter scope are packaging systems and processing equipment used in the preparation, storage, and manufacture of sterile pharmaceutical products. Examples include containers for active pharmaceutical ingredients and containers for product intermediate or final bulk product.

Outside the chapter scope are packages used for sterile diagnostic products or medical devices, and some packages used for sterile drug/device combination products.

Outside the chapter scope are products having a primary package composed of porous barrier package materials, i.e., materials designed with pores or openings to allow volumetric air flow while preventing airborne microbial contamination.

3. LEAKS AND LEAKAGE RATE

Leaks are commonly conceptualized as holes of a defined diameter, or channels of distinctive diameter and length, although leaks that occur naturally are generally complex, multicavity tortuous paths and are rarely uniform in size or shape. Even artificially created leaks such as laser-drilled defects (also called holes) used for leak-test method development and validation are irregular in size, shape, and depth. When stating the size of a leak, it is important to define the measurement approach. In some cases leaks are measured dimensionally, but quite often, leak size is determined based on gaseous leakage rate. For example, a package wall laser-drilled defect having a nominal diameter of 5 ± 2 µm may have been size-certified by matching the airflow rate through the drilled defect to that of a 5 ± 2 µm hole present in a thin metal plate reference standard when pressurized with dry air at specified differential pressure and temperature conditions.

Gaseous leakage rate is a measure of the rate of gas flow (in mass or volume units) that passes through a leak path under specific conditions of temperature and the concentration or pressure differential across the barrier wall. Therefore, gaseous leakage rate has dimensions of pressure multiplied by volume, divided by time. The international standard SI nomenclature is pascal cubic meter per second ($Pa \cdot m^3 \cdot s^{-1}$). These leakage measurement units refer to the quantity of leaking gas ($Pa \cdot m^3$) per unit of time. When a leakage rate is described and no test conditions are noted, standard conditions of one standard atmosphere differential pressure with dry air at 25° are assumed. For a more complete discussion of gaseous leakage rates and units of measure refer to reference *1*.

Unintentional leaks in packages are often detected or sized using gas as a tracer element. Given a situation in which a tracer gas partial pressure difference exists across the package barrier wall and no absolute pressure difference exists, gaseous leakage is predominantly diffusional in nature as the tracer gas moves from a region of higher concentration to a region of lower concentration. For example, the headspace in a vial package low in oxygen concentration and at ambient pressure at time of closure will exhibit a rise in headspace oxygen concentration over time as a function of diffusion rate (relative to package leak size) plus permeation rate (relative to permeability through the package). Such a change can be monitored instrumentally, as is discussed later in the chapter.

Given the situation in which an absolute pressure difference exists across the package barrier wall, gas leakage through package gaps is more rapid (flux being primarily convective) as gas moves from the higher pressure region to one of lower pressure. For most package materials, the permeation rate of the gas of concern through the package wall is insignificant in comparison. In this example, the rate of leakage into the package is determined by monitoring the change in headspace absolute pressure as a function of time.

For many instrumental leak test methods described in this chapter, gas flow into or out of package leaks is induced by exerting a pressure gradient across the package. In this way, a wide range of leak types and sizes can be identified.

Liquid leakage rate is a measure of the volume of liquid that moves through a leak path as a function of time under specified conditions of temperature and absolute differential pressure across the barrier wall. Liquid movement through a leak path occurs only when leak size/shape, package materials of construction, the absence of leak obstruction, tracer liquid composition, and test parameters all work together. All sterile product–packages within the chapter scope are intended to prevent liquid leakage and block microbial entry, thus it is the absence of liquid leakage flow or the absence of liquid in the leak path, rather than the rate at which liquid leakage occurs that is typically verified in relevant package leak tests. Liquid leakage rate measurements are only useful in measuring larger size leaks.

4. CLOSURE TYPE AND MECHANICS

An understanding of closure mechanics makes it possible to better characterize, monitor, and test packages for integrity. This section discusses various closure systems and how each type functions to ensure package integrity.

4.1 Physically Mated Closures

Closure can be achieved by the close physical mating of two surfaces that often are dissimilar in material composition. Examples include the interference fit of a plunger inserted in a syringe barrel, the compression fit of an elastomeric closure

capped onto a vial finish surface, and the application force of a screw-cap torqued onto a bottle. Physically mated surfaces are not bonded together; therefore, a tiny gap exists even between well-closed components. Nevertheless, when properly designed and assembled, closure systems fit together such that liquid leakage (and microbial ingress) is prevented and gas migration is limited. Regarding screw-thread closures such as those used for ophthalmic-product dropper bottles, the barrier to leakage is afforded by inner cap surfaces pressing against the package opening, in some cases aided by a secondary gasket or plug. The winding path afforded by the threads of a screw-cap does not provide an optimal barrier to gas or liquid leakage, or to microbial ingress in the event of liquid presence in the cap threads.

4.2 Physicochemically Bonded Closures

Seals are formed when two similar or dissimilar surfaces are physicochemically bonded together. One example is the formation and sealing of contiguous containers from a single material (e.g., glass or plastic ampules). In other form, fill, and seal systems, sheets of material are mated by means of a heat or ultrasonic welding process. Two dissimilar materials may be joined using an intermediate bonding material. Fully fused seals inherently block liquid leakage and microbial ingress; however, gaseous leakage and permeation may occur.

4.3 Multiple-Dose Package Closures

Multiple-dose package closures are designed to allow product access while limiting microbial ingress and product leakage between doses. For example, elastomeric closures for parenteral products requiring needle-puncture access are designed to offer reseal protection against microbial ingress and product leakage. Some multiple-dose ophthalmic dosage form package closures are designed with filters, plugs, or other mechanical means that allow the product to be dispensed while restricting microbial ingress and product leakage. For example, ophthalmic product–package closure systems have been designed to automatically pinch shut between intermittent dosing to limit microbial entry and product loss.

5. PRODUCT–PACKAGE QUALITY REQUIREMENTS AND THE MAXIMUM ALLOWABLE LEAKAGE LIMIT

As noted in *Introduction*, package integrity is necessary to maintain product critical quality attributes within physicochemical label-claim specifications and to ensure product sterility until time of use. Detrimental contaminants include microorganisms and any substances that threaten patient safety or product quality. Product leakage can cause a product to fail content or potency specification limits. For certain products to maintain product physicochemical stability, the package needs to maintain a headspace of nonreactive gases and/or low water vapor content, sealed under atmospheric or reduced-pressure conditions. Headspace vacuum conditions may also be necessary to facilitate product ease of use, e.g., product reconstitution using a diluent injected into the container.

Most package types display very low but definite gaseous leakage flow through the gap that exists even between well-fitted closures. Therefore, it is not practical to require that packages be absolutely leak-free. Rather, it is the significance of leakage in relation to product quality that needs to be considered. In other words, the package should not permit leakage beyond the product's maximum allowable leakage limit. Such leaks of concern should be absent.

Identifying the maximum allowable leakage limit for a product–package is a science- and risk-based decision. The smaller the leak path, the less likely the product can escape and the less likely microorganisms or other contaminants can enter. Eventually, leak paths may be so small that only headspace gas exchange is realistically possible. Package construction and assembly, package contents, and the range of environments a given product–package may be exposed to during its life cycle are to be considered when specifying the maximum allowable leakage limit.

There are two major product–package quality requirement categories used when specifying the maximum allowable leakage limit and one subcategory that applies only to multiple-dose packages. These are discussed below.

5.1 Sterility and Product Formulation Content must be Preserved; Gas Headspace Content Preservation is not Required

This category includes product–packages for which the maximum allowable leakage limit correlates to the prevention of product formulation escape, or product contamination by external liquid or solid matter or by microorganisms, while gas headspace preservation (i.e., ambient pressure air) is of no concern. The smallest leak paths that allow only limited gas exchange are irrelevant as they pose no real risk to product quality.

Considerable published research exists exploring rigid package leaks and their relationship to risk of aqueous solution leakage and/or microbial ingress. A key study series found orifice leaks of approximately 0.1 µm in nominal diameter (using micropipettes) placed in rigid packages demonstrate a small risk of aqueous liquid passage, while orifice leaks as small as approximately 0.3 µm in nominal diameter first demonstrate some risk of microbial ingress by liquid challenge (*2,3*). For a summary of similar studies comparing risks of microbial ingress and liquid leakage to leak size and type, the reader may refer to reference *4*.

Given this body of evidence, a maximum allowable leakage limit of less than 6×10^{-6} mbar · L/s (measured by helium mass spectrometry in the vacuum mode) can be adopted for products in this category packaged in rigid container–closure systems. This leakage rate equates to the presence of an orifice of nominal diameter of between 0.1 and 0.3 µm. At this leakage rate, the probability of microbial ingress was determined to be <0.10 (*2*). Selecting this conservative maximum allowable leakage limit will ensure a low risk of microbial ingress and liquid leakage and can eliminate the need to perform additional microbial ingress or liquid challenge studies as a function of leak size.

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For other container systems such as those made using flexible materials or those with complex, lengthy closure/seal interfaces, or those meant to contain a product of markedly greater leakage potential, the risk of microbial ingress or liquid passage through leak paths is not as widely publicized or perhaps understood. In such cases, where the relationship between defect size/type to the risks of microbial ingress and/or liquid passage is less prescriptive, a study exploring these relationships could be useful. Test results can be used to establish a meaningful maximum allowable leakage limit for the given product–package system, which can be employed for package integrity verification by other validated leak test methods of choice. Once established, this maximum allowable leakage limit can be applied to similar product–packages with appropriate justification.

Finally, before classifying a product–package in this category, one may consider the potential impact of product life cycle processing, storage, distribution and use scenarios on package integrity. For example, elastomeric closures have been found to shrink and lose their viscoelastic properties during ultra-cold storage (≤–80°) to such an extent that gas influx into stoppered vial packages may occur. During warming, package closure is restored, trapping gases and notably raising internal package pressure. In such cases, gas headspace preservation may be a product quality concern, even if the product does not require specific headspace content or pressure for optimum stability.

5.2 Sterility, Product Formulation Content, and Gas Headspace Content must be Preserved

The second category includes product–packages for which the package should prevent product formulation escape and product contamination by external liquid or solid matter or by microorganisms, but in addition, the package must preserve the gas headspace content or absolute pressure. Preservation of headspace content and/or pressure is needed to maintain product stability within physicochemical specification limits, and/or to aid end-user product access. Thus, the maximum allowable leakage limit for such products is likely more stringent than that described in the first category. Although outside the chapter scope, the influence of gas permeation through the package itself may also need to be considered when establishing the maximum allowable leakage limit as permeation plus leakage can impact package headspace content.

The maximum allowable leakage limit for products in this category may be expressed in terms of the maximum allowable package headspace content or pressure change as a function of time. This limit, established for each product–package system, may be applied to other similar product–packages systems with appropriate justification.

5.3 Sterility must be Preserved; Product Access is Required

This subcategory represents a quality requirement applicable only to multiple-dose product–packages included in either of the above two categories. Once the product–package has reached the end-user and the closure has been activated or otherwise compromised to allow dosage access and delivery, the maximum allowable leakage limit at this life cycle phase (called the in-use maximum allowable leakage limit) is defined in terms of microbial ingress and product loss prevention between and during dosage access. For example, elastomeric closures of multiple-dose vials or cartridges containing antimicrobial-preserved parenteral products are designed to afford reseal protection against microbial ingress and product formulation leakage as product is accessed via needle puncture as well as between doses.

To establish the in-use maximum allowable leakage limit for multiple-dose package closure systems, a study will likely be required to explore the relationship between product access attempts, product loss risk and/or microbial ingress risk, versus leakage measurement by an alternative adequately sensitive leak test method of choice. These data can be used to establish a meaningful in-use maximum allowable leakage limit expressed in units of measure reflective of the preferred leak test method and that will assure that product loss and microbial ingress risk during use is minimal. The in-use maximum allowable leakage limit established for a given product–package may be applied to other similar product–packages systems with appropriate justification.

6. INHERENT PACKAGE INTEGRITY AND THE PACKAGE INTEGRITY PROFILE

Inherent package integrity is the leakage characteristic of a well-assembled container–closure system using no-defect package components. Inherent package integrity is first determined during product–package development and qualification and is a measure of the leak tightness of a container–closure system, given anticipated variables of material composition, dimension, processing, and assembly. Inherent package integrity may also be determined as a function of anticipated final product storage, distribution, and use. Acceptable inherent package integrity for a container–closure system conforms to the specific product–package maximum allowable leakage limit. Inherent package integrity is expressed in terms that allow a meaningful comparison to the maximum allowable leakage limit.

Confirmation that the inherent package integrity conforms to the maximum allowable leakage limit is the first step in product–package integrity verification. Verification of package integrity continues throughout the product life cycle. The package integrity profile is an ongoing database of product life cycle package leak and seal quality test results. This profile provides information regarding package integrity given operative variations in package component design and material; package assembly and processing; and product storage, distribution, and stability. These concepts are more fully explored in *Package Integrity Testing in the Product Life Cycle—Test Method Selection and Validation* ⟨1207.1⟩*, Test Instrument Qualification, Method Development, and Method Validation*.

In summary, a product–package system having integrity is one in which the inherent package integrity conforms to the required product–package maximum allowable leakage limit. Further, the package integrity profile database operates as a risk management tool to ensure that finished product container–closure systems are intact, able to block microbial ingress, restrict loss of product contents including critical headspace gases, and prevent entry of detrimental gases or other substances, thus ensuring that the product meets all relevant physicochemical and microbiological label-claim specifications through expiry and final end-use.

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GLOSSARY

For definitions of container, materials of construction, packaging component, packaging system, primary packaging component, and secondary packaging component, see *Packaging and Storage Requirements* ⟨659⟩. In the context of this chapter and its subchapters, the following definitions relevant to packaging and package integrity methods, seal and closure mechanisms apply. For definitions of specific leak test and seal quality test methods, refer to ⟨1207.2⟩ and ⟨1207.3⟩, respectively.

Accuracy: The accuracy of a leak test method is a measure of the ability of the method to correctly differentiate packages that leak above the claimed detection limit from those that leak below this limit (do not leak); a measure of false positive and negative occurrence. Alternatively, for those methods that deliver an outcome that is a direct quantitative measure of gas leakage rate (or of gas content or pressure), accuracy is a measure of the method's ability to produce an outcome comparable to a true standard, such as a nationally recognized gas standard.

Container–closure integrity: Container–closure integrity is the ability of a package to prevent product loss, to block microorganism ingress, and to limit entry of detrimental gases or other substances, thus ensuring that the product meets all necessary safety and quality standards. Synonymous with *Package integrity*.

Container–closure integrity test: A container–closure integrity test is any package leak test (either physicochemical or microbiological) that detects the presence of a package breach or gap. Some tests may also be able to identify the leak magnitude and/or location. The term container–closure integrity test is synonymous with package leak test or package integrity test.

Container–closure system: See *Packaging and Storage Requirements* ⟨659⟩*, General Definitions, Packaging System*.

Detection limit: The leak test detection limit is a measure of test method sensitivity. The detection limit is the smallest leakage rate (or leak size) that a leak test method can reliably detect. Also called limit of detection.

Deterministic leak test method: A deterministic leak test method is one in which the leakage event being detected or measured is based on phenomena that follow a predictable chain of events. In addition, the measure of leak detection is based on physicochemical technologies that are readily controlled and monitored, yielding objective quantitative data.

In-use maximum allowable leakage limit: See *Maximum allowable leaking limit*.

Inherent package integrity: Inherent package integrity is the leakage rate (or leak size) of a well-assembled container–closure system using no-defect package components. Inherent package integrity is a measure of the leak tightness of a container–closure system, given anticipated variables of material composition, dimension, processing, assembly; package storage, distribution and use.

Leak: A leak is a breach in a package wall or a gap between package components that is capable of permitting the passage of gas, liquid, or solid matter. Leak is synonymous with leak path.

Leakage: Leakage is the unintentional escape or entry of matter (solid, liquid, or gas) through a breach in the package wall or through a gap between package components. Leakage can also refer to the substance that enters or escapes from a compromised package. For example, "Leakage from the cracked container stained the package label."

Leakage rate: Gaseous leakage rate is a measure of the rate of gas flow (in mass or volume units) that passes through a leak path under specific conditions of temperature and absolute pressure or concentration differential. Leakage rate has dimensions of pressure multiplied by volume, divided by time. For example, the international standard SI nomenclature is pascal cubic meter per second ($Pa \cdot m^3 \cdot s^{-1}$). Other common units of measure include standard cubic centimeters per second (std $\cdot$ $cm^3 \cdot s^{-1}$ or sccs) and mbar liters per second ($mbar \cdot L \cdot s^{-1}$). Liquid leakage rate is a measure of the volume of liquid that moves through a leak path as a function of time under specified conditions of temperature and absolute differential pressure across the barrier wall. Liquid leakage rate measurement, possible for larger leak tests, requires that leak size, materials of construction; absence of leak obstruction; tracer liquid composition; and test parameters work together to ensure liquid movement through the leak path.

Linearity: Leak test method linearity is the ability of the method to elicit test results that are mathematically proportional to leak path size or leakage rate.

Master: A master is a package prototype, model, or facsimile made to simulate an actual package in shape and design. Masters may be made of solid plastic or metal, or they may be simply a designated container–closure unit. Masters are designed to simulate a no-leaking package, and are often used in leak test system suitability tests to verify instrument performance.

Maximum allowable leakage limit: The maximum allowable leakage limit is the greatest leakage rate (or leak size) tolerable for a given product–package that poses no risk to product safety and no or inconsequential impact on product quality. The maximum allowable leakage limit for a sterile pharmaceutical dosage form package will ensure the content's sterility, preserve product contents, and prevent entry by detrimental gases or other substances, thus ensuring that the product meets relevant physicochemical and microbiological specifications through expiry and use. For multiple-dose product–packages, the in-use maximum allowable leakage limit is defined as the degree of protection demanded of the closure to limit microbial ingress and product formulation leakage between and during dosage access.

Microbiological challenge test: A microbiological challenge test is a package leak test whereby package integrity is evaluated by exposing containers filled with growth-supportive media to microorganisms suspended in submersion media (a

liquid-borne challenge test). Leakage is evidenced by the subsequent growth of the challenge microorganisms in the package contents. Synonymous with microbial challenge test.

Negative control: A negative control is a package with no known leak. Negative controls used for leak test method development and validation studies represent packages optimally assembled using normally processed components. Negative controls should duplicate the container–closure system of the product under integrity investigation. For some methods, it may be necessary for negative controls to simulate test product headspace and formulation content as well.

Nonporous: Nonporous packaging does not have pores or openings to allow volumetric air flow. In other words, NMT a small fraction of molecules is able to pass through any one hole. Nonporous materials may be impermeable, semi-permeable, or permeable to the passage of fluid through the package barrier wall.

Nominal diameter: In the context of this chapter, nominal diameter is a means of expressing the size of a package leak. Package leaks are typically irregular tortuous paths or matrices that cross a package wall or barrier. Such leaks are difficult to size in accurate or meaningful terms. The nominal diameter of a leak path is defined as the width of an orifice of relatively short depth, through which gas (e.g., dry air) at equivalent airflow rate may pass when subject to one atmosphere differential pressure at controlled temperature conditions.

Package integrity: See *Container–closure integrity*.

Package integrity test: See *Container–closure integrity test*.

Package integrity profile: The package integrity profile is a database of product life cycle package leak and seal quality test results that denotes product–package integrity given operative variations in package component design and material; package assembly and processing; and product storage, distribution, and stability.

Package leak test: See *Container–closure integrity test*.

Package seal quality: Package seal quality relates to the consistency of a package seal's performance within required specification limits. Examples of package seal quality attributes include heat seal bond strength and capped vial package residual seal force.

Package seal quality test: A package seal quality test is used to characterize and monitor the quality of a product–package seal or closure system to ensure that package assembly is consistently kept within established limits. Package seal quality tests are not and cannot substitute for leak tests. However, they can provide some assurance of the package's ability to maintain integrity by monitoring a characteristic of the seal itself, the package materials, the package components, and/or the processes required to create the seal or closure mechanism. Examples include the seal peel force test and the capped vial package residual seal force test.

Permeation: Permeation is the passage of fluid into, through, and out of a nonporous package wall. Permeation, not leakage, occurs when the package barrier has no holes large enough for more than a small fraction of molecules to pass through any one hole.

Physicochemical package integrity test: A physicochemical package integrity test is a leak test that detects the presence of a package leak, or detects/measures package leakage rate, via physical or chemical means. All leak test methods that do not use microorganisms for leak detection are physicochemical leak test methods.

Porous: A porous package or package material has pores or openings to allow volumetric air flow while still blocking airborne microbial passage. Examples include coated paper or spun-bonded polyolefin barrier materials that permit package penetration by ethylene oxide gas or steam.

Positive control: A positive control is a package with a known, intentional defect. Positive controls used for leak test method development and validation studies should duplicate study negative controls in terms of materials of construction, package assembly, and component processing. Positive controls are used during leak test method development and validation. Some methods require the use of positive controls during routine testing as well.

Precision: Leak test method precision is a measure of the method's ability to yield reliable, repeatable data. Precision includes repeatability (repeat testing of a single homogeneous test sample population set), ruggedness (within laboratory tests performed by multiple operators on multiple days, using multiple instruments; also known as intermediate precision), and reproducibility (tests among multiple laboratories).

Probabilistic leak test method: A probabilistic leak test method is the converse of a deterministic leak test method, being stochastic in nature. Probabilistic tests rely on a series of sequential and/or simultaneous events, each associated with random outcomes described by probability distributions. Thus, the findings are associated with uncertainties that necessitate large sample sizes and rigorous test-condition controls to obtain meaningful results. Typically, sample size and test condition rigor are inversely related to leak size.

Product: The pharmaceutical product includes the pharmaceutical formulation as well as the packaged headspace, which may consist of ambient air or nonreactive gases with specified water-vapor content under full or sub-atmospheric pressure conditions.

Product–package: The product–package includes the primary package with critical secondary components (the container–closure system) plus the packaged product (the contents).

Qualitative measure of analysis: A qualitative measure of analysis for leak testing is a measurement approach based on a subjective evaluation of some quality, attribute, or characteristic of the test sample. Visual inspection is an example of a qualitative measure of analysis.

Quantitation limit: The quantitation limit is a leak test method characteristic defining the lowest leakage rate or leak size that can be differentiated with accuracy and precision under the stated experimental conditions.

Quantitative measure of analysis: A quantitative measure of analysis for leak testing is a measurement approach based on objective, numeric data that either directly or indirectly correlates with leak presence, leak location, or leakage rate. Examples include the mass-of-gas-per-time reading generated by the helium mass spectrometry tracer-gas leak test, or the pressure reading as a function of test time measurement produced by the vacuum-decay method.

Range: The range of a leak test method is that interval between the smallest to largest leak size (or leakage rate) that can be detected by a given leak test method with a suitable level of accuracy and precision.

Robustness: Robustness of a leak test method is the method's ability to accurately identify leaking versus nonleaking packages despite small but deliberate variations in procedural parameters, providing an indication of the method's suitability during normal usage.

Specificity: The specificity of a leak test method is the ability of the method to accurately differentiate leaking and nonleaking packages, despite interfering factors that may cause false detection.

System suitability: System suitability is a manner of ensuring that the leak test method including all factors, which may be subject to variability, that may impact test results (such as instrumentation, analysts, test sample preparation steps, and the test environment) are adequately controlled and maintained in such a fashion that the method is rugged and robust.

System suitability test: A system suitability test is a test to verify that the leak test method and all key factors that may impact test results are correctly controlled and set prior to method performance.

Tortuous path: As applied to leaks, a tortuous path is a convoluted, complex leakage pathway. Most naturally occurring leaks, such as cracks and tears, are tortuous in nature, rather than pristine holes. As applied to sealing mechanisms, a sealing material that has tortuous barrier qualities can block microbial entry. [NOTE—The winding path afforded by the threads of a screw-cap (e.g., an ophthalmic dropper bottle closure) does not provide an optimal barrier to gas or liquid leakage, nor does it provide an optimal barrier to microbial ingress in the event of a liquid presence in the cap threads.]

Type defect: A type defect is a positive-control package that represents realistic package flaws. Type-defect positive controls may be included in leak test method feasibility and development studies before method validation. An example of a type defect is a heat seal wrinkle or a loose cap. Type defects are inherently irregular in size and shape and are often described qualitatively instead of being described in terms of leak size or leakage rate.