BRIEFING

〈1207〉 **Sterile Product Packaging—Integrity Evaluation** *USP 37* page 1132. Extensive revisions to general information chapter *Sterile Product Packaging—Integrity Evaluation* 〈1207〉 are presented for public comment in this issue of the *Pharmacopeial Forum*. The original content of chapter 〈1207〉 has been revised and also subdivided into four related chapters (〈1207〉, 〈1207.1〉, 〈1207.2〉, and 〈1207.3〉) and represents the combined efforts of the USP Microbiology Expert Committee and the USP Packaging, Storage, and Distribution Expert Committee. A Stimuli article, which also appears in this issue of the *Pharmacopeial Forum*, provides the background, history, and rationale for the revisions and subdivision of the content.

Additionally, minor editorial changes have been made to update the chapter to current *USP* style.

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Comment deadline: November 30, 2014

〈1207〉 STERILE PRODUCT PACKAGING—INTEGRITY EVALUATION

Change to read:

INTRODUCTION

Chapter *Sterile Product Packaging—Integrity Evaluation* 〈1207〉 provides an overview of “leak test”

methodologies (also termed technologies, approaches, or methods) as well as “package seal quality tests” useful for verification of sterile product package integrity. More detailed recommendations for the selection, qualification, and use of leak test methods are presented in three subchapters that address these specific topics:

- *Package Integrity and Test Method Selection* 〈1207.1〉
- *Package Integrity Leak Test Technologies* 〈1207.2〉
- *Package Seal Quality Test Methods* 〈1207.3〉

At the end of chapter 〈1207〉, the *Appendix: Definitions* section defines terms as they are used in the context of this set of four general information chapters.

“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. These contaminants may include microorgansims, reactive gases, and other substances. The “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 and under full or subatmospheric pressure conditions. Sterile product package integrity is synonymous with “container–closure integrity” and will be referred to as “package integrity” throughout this chapter. A package is considered integral if it allows no leakage greater than the package “maximum allowable leakage limit”. 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, but also “secondary packaging components”, vital to ensuring correct package assembly, for example, the aluminum cap used to seal a stoppered vial package. In some cases, the “packaging system” may also include items such as a lidded tray that is used to protect the exterior sterility of each item within the kit.

The methods described are chiefly used to test the container–closure systems for sterile pharmaceutical dosage forms; such packaging systems generally consist of nonporous components that are either rigid or flexible. However, the same test concepts and methods can be applied to any pharmaceutical product packaging system, including but not limited to active pharmaceutical ingredient containers; containers for intermediates or final formulation bulk volumes; and drug/device combination product–packages. Nonporous packages may be used for other types of sterile products as well, including sterile diagnostic products or medical devices. Sterile medical devices and diagnostic products are not subject to the recommendations of this chapter; however, the concepts presented for testing pharmaceutical product nonporous packages may be applied.

This chapter does not address package integrity test methods relevant to porous barrier packages that are designed solely to prevent airborne microbial contamination. Examples of these packages include a semi-rigid tray closed with a porous lidding material and a bag with a porous barrier material component. Such packaging systems may be used to contain sterile pharmaceutical products, and for this reason they are mentioned throughout the chapter as packages that must meet container–closure integrity requirements. However, this chapter does not attempt to address porous barrier packaging tests; therefore, the reader is advised to consult resources relevant to the medical device packaging industry for appropriate integrity tests of porous barrier packaging systems.

“Package integrity tests”, also called “container–closure integrity tests”, are “leak test methods”. Package permeation methodologies are not described. A “leak test” is a method that detects the presence of (and in some cases, the magnitude or location of) a defect in a package; the defect is capable of permitting loss of product contents or critical headspace gases, and/or capable of permitting entry of liquids, reactive gases, microorganisms, or nonviable particulates. “Package seal-quality tests” are evaluations used to characterize and monitor the quality and consistency of a package seal parameter. These tests provide some assurance of the package's ability to remain integral; an example is the heat seal peel force tests. Seal-quality tests are not leak tests but can play a valuable role in ensuring package integrity by monitoring a characteristic of the seal itself or the materials, components, and/or processes required to create the seal.

Integrity test methods vary in terms of detection limit, reliability, and application, and therefore are not appropriate for all package leak testing uses. Selection criteria for package integrity test methods, as well as method comparison aids, are presented below to guide the user in the selection process.

Any leak test or package seal-quality test, even the standard test methods, requires optimization for each product–package application. Validation of the final leak test method is required to demonstrate test method detection limit, accuracy, and precision. Package integrity test method application continues throughout the product life cycle, starting with product development and continuing through marketed product stability studies.

PACKAGE INTEGRITY CONCEPTS

Sterile product–package integrity is necessary to maintain 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 product sterility and patient safety. Excessive product loss includes leakage that exceeds specification limits for product content or potency. For certain products to maintain product physicochemical stability, the package needs to maintain a headspace of nonreactive gases and/or gases with low vapor content, sealed under atmospheric or reduced-pressure conditions. Reduced-pressure conditions may also be necessary to facilitate product ease of use, e.g., product reconstitution.

Sterile product–packages must demonstrate satisfactory container–closure integrity. However, it is not realistic or practical to require packages to be absolutely integral—in other words, not allowing even the slightest gas escape—because most package types exhibit at least miniscule gaseous leakage plus permeation. Leakage differs from permeation. Leakage is the movement of liquids or gases through a breach in the package wall or a gap between package components. Permeation is the passage of matter through the package wall itself. Both leakage and permeation play important roles in parenteral product–package performance. Although only leakage is relevant to a package's ability to prevent microbial ingress, leakage plus permeation determines a package's ability to retain critical headspace and volatile product contents.

To illustrate, a stoppered glass vial exemplifies a package type made of multiple components mechanically fitted together in which permeation through the elastomeric stopper is possible, as is gas leakage at the stopper–vial interface. All packages with polymeric or elastomeric component(s) exhibit some degree of gas permeation, and all packages mechanically fitted together from multiple components also leak to some degree. Even package components that are chemically bonded together with adhesives will permit some permeation. A well-sealed glass ampul is a unique package design that should demonstrate no measureable leakage or permeation.

In many cases, the distinction between leakage and permeation for a well-closed package can be difficult or impractical to establish. Because most package types exhibit at least some small degree of gas exchange, it is more meaningful to require that packages stay within the maximum allowable leakage limit specific for the package design and provide the level of protection necessary for the product contents. For instance, seals meant to prevent loss of vacuum or inert gas headspace until product expiry may require a more stringent “maximum allowable leakage limit” than seals solely intended to prevent liquid leakage and microbial ingress. In contrast, pharmaceutical-containing trays that are closed with porous barrier lidding designed merely to keep out airborne microbes and debris do not need to meet the maximum allowable leakage limit of nonporous packages that must prevent liquid leakage.

In summary, an integral package is one that conforms to specific product–package maximum allowable leakage limits, and in so doing, also blocks microbial ingress, restricts loss of product contents, and prevents entry of detrimental gases or other substances, thus ensuring that the product meets physicochemical and microbiological label-claim specifications.

LEAKS AND LEAKAGE

“Leaks” are commonly perceived as holes of a certain diameter, or channels of a certain diameter and length.

Such terminology helps to conceptualize defects, although leaks that occur naturally are rarely dimensionally uniform holes or channels. Generally, they are complex, multicavity “tortuous paths”. Even artificially created leaks, such as laser-drilled holes used for leak-test method development and validation, are dimensionally irregular. When stating the size of a leak, it is important to define the measurement approach taken. In some cases leaks are measured dimensionally, but quite often, leak size is stated in terms of its leakage rate. For example, to say a laser-drilled hole in a package wall has a nominal diameter of 5 µm may actually mean that the airflow rate through the drilled defect matches that of a pristine 5-µm hole in a thin metal plate reference standard when pressurized with dry air at specified differential pressure and temperature conditions.

“Leakage” 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 pressure. Therefore, 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. To express SI leakage units in mass flow terms, the pressure and temperature must be at standard pressure and temperature, which are 101 kPa (760 torr) and 0° (273 K) (*1*). *Table 1* lists several other common units of measure for leak rate. When expressing leakage volumetrically, the test pressure and temperature conditions are specified (*1*).

Table 1. Mass Flow Conversion Factors for Common Leak-Rate Units[a]

Pascal Cubic Meter Per Second	Standard Cubic Centimeter Per Second	Mole Liter Per Second	Millibar Liter Per Second	Torr Liter Per Second
$Pa \cdot m^3 \cdot s^{-1}$	Std $cm^3 \cdot s^{-1}$ (Alternatively, sccs)	$mol \cdot s^{-1}$	$mb \cdot L \cdot s^{-1}$	$torr \cdot L \cdot s^{-1}$
1	9.87 (≅10)	4.40×10^{-4}	1.00×10^{1}	7.50

[a] Jackson et al. (*1*).

REFERENCE

1. Jackson CN, Sherlock CN, Moore PO, editors. In: Nondestructive testing handbook. 3rd ed. Vol. 1. Leak testing. Columbus, OH: The American Society for Nondestructive Testing; 1997.

APPENDIX: DEFINITIONS

For definitions of container, materials of construction, packaging component, packaging system, primary packaging component, and secondary packaging component, see chapter *Packaging and Storage Requirements* 〈659〉. In the context of chapter 〈1207〉 and its subchapters, the following definitions relevant to packaging and package integrity methods apply. For definitions relevant to seal and closure mechanisms, refer to 〈1207.1〉. For definitions of specific leak test and seal quality test methods, refer to chapters 〈1207.2〉 and 〈1207.3〉, respectively.

Acceptance criterion: The leak test method acceptance criterion is the leak test method pass/fail limit. Test samples that meet the acceptance criterion are considered to be free of measureable leaks as determined by the given method. For example, a vacuum-decay leak test acceptance criterion is defined as the maximum allowable pressure-rise reading at the end of the timed test cycle. A bubble emission test's acceptance criterion may be expressed as the absence of a visible, continuous stream of bubbles emitted from a test package during a defined period of test sample submersion and vacuum exposure.

Accuracy: The accuracy of a leak test method is the method's false-detection probability, in other words, the ability of the method to correctly differentiate packages that leak above the limit of detection from those that

leak below this limit (i.e., do not leak).

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.

Container–closure integrity test: A container–closure integrity test is any package leak test (either physicochemical or microbiological) that detects the presence and/or size of a breach or gap in a package that is capable of permitting loss of product contents or critical headspace gases, and/or capable of permitting entry of microorganisms, reactive gases, or other substances. The term container–closure integrity test is synonymous with “package leak test” or “package integrity test”.

Container–closure system: See *Packaging System* in *General Definitions* (chapter 〈 659 〉).

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.

Largest leak detection capability: A leak test method's largest leak detection capability is the method's ability to detect larger leaks of a given size or defect type (i.e., the upper limit of the leak detection range).

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 or liquid. Leak is synonymous with “leak path”.

Leakage: This term has two distinct meanings: 1) Leakage 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 pressure. 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 ($Pa \cdot m^3 \cdot s^{-1}$). 2) Leakage is the actual product that escapes from a defective or unclosed package. For example, “Leakage from the container stained the package label.”

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

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 stability. The maximum allowable leakage limit for a sterile pharmaceutical dosage form package is the leakage rate (or leak size) that will ensure the content's sterility, preserve product contents, and prevent entry by detrimental gases or other substances, thus ensuring that the product meets physicochemical and microbiological specifications.

Microbial grow-through: Microbial grow-through is a process whereby microorganisms actively enter a package by multiplying along package surfaces, obtaining nourishment from product formulation residues or other contaminants left on package surfaces, or (less likely) from the surfaces themselves.

Microbial grow-through controls: Microbial grow-through controls are positive controls used to evaluate the risk posed by microbial grow-through via product residues left on multi-dose package closure components or filter media. Such positive controls are specifically designed to appropriately represent the given product–package system.

Microbial passive entry: Microbial passive entry is a process whereby microorganisms are mechanically swept through a leak path into a package via a liquid or gas carrier.

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 growth of microorganisms in the package contents.

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 that were typically assembled using normally processed components.

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

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, other than leakage prevention. 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 a check used to characterize and monitor the quality of various product–package seals to ensure that package assembly is consistently kept within established limits, thereby providing some assurance of the package's ability to remain integral. Examples include the peel force test for heat seals and the residual seal force test for capped vial packages.

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.

Positive control: A positive control is a package with a known, intentional leak. Positive controls used for leak test method development and validation studies should duplicate those negative controls used for the same studies in terms of materials of construction, package assembly, and component processing. Positive controls are included for defect type and for larger-size defects (used for method development), as well as smallest-size defects (used for method development and validation studies). Microbial grow-through positive controls are used for microbiological challenge method development, validation, and routine testing of certain packaging systems uniquely at risk for microbial entry by grow-through processes.

Precision: The precision of a leak test method is the ability of the method to yield reliable, repeatable data within and among analysts, instruments, and labs.

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; therefore, reliable and predictable probabilistic leak test methods may prove more difficult to design, develop, validate, and implement, compared with deterministic methods.

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 subatmospheric pressure conditions.

Product–package: The product–package includes the primary package or container–closure system plus the product 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.

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 volume-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.

Robustness: The robustness of a leak test method relates to the method's ability to accurately identify leaking versus nonleaking packages, given the test conditions bracketing optimal or normal test specifications.

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

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. For example, a breathable porous lidding material sealed on a plastic tray offers a barrier to airborne microbial ingress via the tortuous filter-like mesh lidding construction. [NOTE—The winding path afforded by the threads of a screw-cap (e.g., an ophthalmic dropper bottle closure) does not provide an effective barrier to gas or liquid leakage, nor does it prevent 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 leak rate.

■2S (*USP38*)

~~[1] A review of physical and microbiological methods related to the evaluation of product packaging integrity appears in *Pharmaceutical Package Integrity*, Parenteral Drug Association's Technical Report No. 27, 1998.~~

~~[2] For more information, see ANSI/AAMI/ISO Standard 11607-2000, 2nd ed., Packaging for Terminally Sterilized Medical Devices.~~

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