Understanding Container Closure Integrity Testing

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Introduction

Understanding container closure integrity systems, reviewing past observations, and following the regulations and guidance documents are excellent ways to establish a compliant container closure integrity assay. This article describes recent changes to the United States Pharmacopeia (USP) <1207>, guidance documents, regulatory observations, common container closure methods, and provides recommendations on developing and validating a compliant container closure integrity test.

Overview

Container Closure Integrity Testing (CCIT) is an assay that evaluates the adequacy of container closure systems to maintain a sterile barrier against potential contaminants. Contaminants that could potentially cross a container closure barrier include microorganisms, reactive gases, and other substances (USP <1207>). Container closure systems should maintain the sterility and product quality of sterile final pharmaceutical, biological, and vaccine products throughout their shelf-life (Ewan, S. et al., 2015).

Container closure systems consist of primary packaging components and secondary packaging components (USP <1207>). Primary packaging components are those components that come into direct contact with the product, such as a glass vial or syringe.

While, secondary packaging components are those components that are vital to ensure correct package assembly, such as aluminum caps over stoppers (USP <1207>).

There are many guidance documents and regulations that govern container closure integrity systems. The following list of guidance documents and regulations is not an all-inclusive list, but these resources provide valuable information.

- Code of Federal Regulations (CFR): 21CFR211.94 Drug Product Containers and Closures- (a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.
- 21CFR211.94 Drug Product Containers and Closures- (b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.
- 21CFR211.94 Drug Product Containers and Closures- (c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such depyrogenation processes shall be validated.
- 21CFR211.94 Drug Product Containers and Closures- (d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.
- European Commission EudraLex- The Rules Governing Medicinal Products in the European Union Annex 1- Manufacture of Sterile Medicinal Products (Annex 1)- 117. “Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.”
- European Commission EudraLex- The Rules Governing Medicinal Products in the European Union Annex 1- Manufacture of Sterile Medicinal Products Volume 4- Part II Basic Requirements for Active Substances used as Starting Materials- 9.20. “Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.”
- International Conference on Harmonisation (ICH) Harmonized Triplicated Guideline, Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products Q5C- Sterility testing or alternatives (e.g. container/closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf-life.

- Guidance for the Industry “Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products (Guidance for Industry, 2008).
- USP <1207> Sterile Product Packaging-Integrity Evaluation,<1207.1>Package Integrity and Test Method Selection,<1207.2>Package Integrity Leak Test Technologies and<1207.3>Package Seal Quality Test Methods
- Parenteral Drug Association (PDA) Technical Report 27
- PDA White Paper: Container Closure Integrity Control versus Integrity Testing during Routine Manufacturing (Ewan, S. et al., 2015)
- US Food and Drug Administration (FDA) Compliance Program Guidance Manual, Chapter 56-Drug Quality Assurance Program 7356. 002A- 09/11/15- (5) Verification of Container and Closures. The physical and chemical characteristics of containers and closures can be critical to the sterility and stability of the finished product. Many containers and closures look alike (color and dimensions), but are made of different materials or have a different surface treatment such as silicone on stoppers and ammonium sulfate on Type I glass.
- FDA Compliance Program Guidance Manual, Chapter 56-Drug Quality Assurance Program 7356.002A- 09/11/15- Evaluate the firm’s procedures for assuring containers and closure consistently meet appropriate specifications. FDA Compliance Program Guidance Manual, Chapter 56-Drug Quality Assurance Program 7356. 002A- 09/11/15- Determine what tests and examinations are done to verify the containers and closures are made of the correct materials with the correct dimensions (critical to ensuring continuing container-closure integrity) and are free of critical defects.
- FDA Compliance Program Guidance Manual, Chapter 56- Drug Quality Assurance Program 7356. 002A- 09/11/15- (6) Container / Closure Integrity. The integrity of the container / closure system is critical to assuring that all units of drug products remain sterile through shipment, storage and use. Leaking containers or closures lead to product contamination.
- FDA’s 1994 Guidance for Industry for the Submission of Sterilization Process Validation in Applications for Human and Veterinary Drug Products- Evaluate the tests and studies performed to demonstrate the integrity of container / closure systems for all sterile drugs, including:
    - Verify that all incoming container-closure components meet specifications, including all appropriate dimensions.
    - Determine studies adequately simulate the stress conditions of the sterilization process, handling and storage.
    - Verify that the units tested in validation are appropriate (e.g., for terminally sterilized drug product, the units selected should be exposed to the maximum sterilization cycles using the production process).
    - Sensitivity of the test is specified.
    - Container-closure integrity is demonstrated during validation and as part of the stability program (in lieu of sterility testing), over the shelf life of the product.

Establishing a proper container closure system is extremely important to product and consumer safety. In addition to the many guidance document sources, many observations have been written by the regulators for violations regarding container closure systems. The following list of observations provides insight on how to avoid the same observations

regarding container closure systems. Observations may be researched on the FDA website, www.fda.gov.

- FDA Warning Letter Dated 24Jun09: “This is a repeat violation of the February 2007 inspection. Your quality control unit (QCU) failed to establish an adequate stability testing program designed to evaluate the integrity of the container-closure system. Specifically, SOP-QC-(Redacted) does not include the storage orientation for liquid products. The stability samples for liquid products should be stored in an upright or inverted orientation in order to test and evaluate the integrity of the bottle seal.” (FDA Warning Letters, 2016)
- FDA Warning Letter Dated 20Jan11: “Your firm failed to ensure your container closure system provided adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product [21 C.F.R. § 211.94(b)]. For example, your firm identified 542 incidences through consumer complaints of product defects such as, leaks, bursts, and premature activation during the period of January 2008 to August 2010. These are critical defects that can impact sterility and stability of your product. Your firm identified that the probable cause was the result of defective materials used in the manufacture of the container closure system. Your response is not adequate since the sampling plans described are not based on appropriate statistical criteria to sufficiently identify these known potential defects, especially given the history of the supplier for this container closure system. Furthermore, your final product inspection procedure and use of a (b)(4) does not appear to be effective in preventing shipments of product with critical defects to the marketplace. Additionally, our data indicates there may be other cases of foreign substances in products manufactured at your facility such as an insect found in the intravenous solution of (Redacted) and dirt reported inside of (b)(4) and the (b)(4) of (Redacted)®. Please provide an evaluation of the suitability of any of these potentially affected lots.” (FDA Warning Letters, 2016)
- FDA Warning Letter Dated 31May13: “Your firm failed to ensure your container closure system provided adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product (21 CFR 211.94(b)). For example, you received consumer complaints identifying at least ten (10) membrane leaks and one hundred fifty-five (155) inadequately-fitting blue caps during the period of November 2011 to March 2013. These are critical defects that can impact the sterility and stability of your products. This is a repeat violation.” (FDA Warning Letters, 2016)
- FDA Warning Letter Dated 02Nov15: “FDA investigators also noted current good manufacturing practices (cGMP) violations at your facility, causing your drug product(s) to be adulterated within the meaning of section 501(a)(2) (B) of the federal food, drug, and cosmetic act (FDCA). The violations include, for example: Your firm failed to establish adequate written procedures designed to assure batch uniformity and integrity of drug products that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch (21 CFR 211.110(a)). Your firm failed to ensure container closure systems provide protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product (21 CFR 211.94(b)).” (FDA Warning Letters, 2016)

- FDA Warning Letter Dated 21APR16: “Puncturing a container compromises the integrity of the container closure system, and each puncture increases the chances of contamination. In response to our observation regarding (b)(4), you indicated that you developed a container closure integrity test for the (b)(4) and plan to demonstrate the sterility of the (b)(4) throughout its expiry. However, this test only confirms the sampled portion is sterile and does not validate the integrity of the container. Additionally, the tested portion may not have detectable microbial contamination after the (b)(4) container loses integrity, but the amount of bacterial endotoxin may still increase. Your proposed corrective action is not adequate to demonstrate container closure integrity. Therefore, your response does not indicate how you will ensure your finished product is sterile and the amount of endotoxin is within an acceptable limit after multiple punctures to the (b)(4) containers.” (FDA Warning Letters, 2016)

  By reviewing past regulatory observations, learning the container closure systems, and following established regulations and guidance documents, a compliant container closure integrity test may be established.

Testing Methods

Container closure integrity testing can be performed in many different ways. All of the testing methods have pros and cons (Gladd, 2014). In addition, some containers, such as ampoules, require 100% integrity testing (Ewan, S. et al., 2015).

The revised USP <1207> series describes several common container closure integrity testing methods. The update removes the requirement to compare the results of other container closure integrity (CCI) assays to the microbial ingress challenge. The chapter divides the tests into two major categories, deterministic and probabilistic. Deterministic methods are less subject to error and provide quantitative results (Gladd, 2014). Probabilistic methods are more uncertainty in the assay results and include the more traditional methods of testing (Gladd, 2014).

The testing methods included in USP <1207.1> were chosen from peer reviewed articles and are supported by the American Society for Testing and Materials (ASTM) (Gladd, 2014). The user may choose from the methods listed or even methods that are not listed as long as the final method is properly validated and optimized for the closure system (Gladd, 2014).

- The deterministic methods include the following:
- Electrical Conductivity and Capacitance Test (HVLD)
- Laser-based Gas Headspace Analysis
- Mass Extraction
- Pressure Decay
- Tracer Gas (vacuum mode)
- Vacuum Decay

The Electrical Conductivity and Capacitance Test is also known as High Voltage Leak Detection (HVLD). This assay looks for leaks in walls of nonporous, rigid or flexible packaging containing liquid or semi-liquid product (e.g. ampoules) (USP <1207.2>). During the assay, a high voltage and high frequency charge is applied across the containerclosure system (White, 2012). A detected leak will cause an increase in current across the high voltage electrodes, triggering the reject mechanism for the leak detector (White, 2012). Key factors for the assay include the voltage level, probe positioning, the container-closure system geometry, the wall thickness, and the product formulation (White, 2012).

The Laser-based Gas Headspace Analysis is typically performed using non-contact methods, such as frequency modulation spectroscopy (White, 2012). During the assay, a near infrared diode laser light passes through the gas headspace region. The light is absorbed as a function of gas concentration and pressure (USP <1207.2>). This absorption information is processed using phase-sensitive detection techniques (USP <1207.2>). A microprocessor analyzes the data and yields the test results (USP <1207.2>).

The Laser-based Gas Headspace Analysis can be used for lyophilized products or oxygen-sensitive liquid products (White, 2012). The gas analysis of the headspace is rapid, on the order of seconds. This method allows for 100% inspection of oxygen sensitive products or products packaged under vacuum (White, 2012). The test is nondestructive and provides quantitative results (USP <1207.2>). Key parameters for the assay include the headspace volume, the package temperature, the headspace pressure, vacuum, and the sensitivity of the headspace analysis instrumentation (White, 2012).

The Mass Extraction assay is nondestructive and quantitative (USP <1207.2>). It can be used for detecting leaks in nonporous, rigid or flexible packages (USP <1207.2>). Packages with a porous component can be tested with the mass extraction assay by masking the porous package component (USP <1207.2>).

The assay is performed by placing the test sample inside a test chamber that is pneumatically connected to a mass extraction leak test system equipped with a vacuum generator package (USP <1207.2>). The chamber is quickly evacuated for a predetermined time to reach a predetermined vacuum level. A series of evacuation cycles are performed, each intended to identify smaller leakage rates (USP <1207.2>). After each cycle, the test system is isolated from the vacuum source and measurements of absolute pressure, pressure decay rate, and/or gas mass flow rate are captured (USP <1207.2>). Readings that are greater than the predetermined limits that were established using negative controls are indicative of container leakage. These readings will trigger the test cycle abort (USP <1207.2>). For those test samples passing all previous larger leak vacuum cycles, a final vacuum is drawn (USP <1207.2>). The mass flow rate is measured with all of the flow from the test chamber directed

through the mass flow sensor. Mass flow that is above a predetermined limit established using negative controls is indicative of container leakage (USP <1207.2>).

The Pressure Decay assay is intended for integrity testing of the gas headspace region of the test sample (nonporous, rigid, or flexible packages) (White, 2012). For this test, the container-closure system is placed in a test fixture that is either pressurized or evacuated (White, 2012). The test chamber is allowed to stabilize, and then the change in pressure or vacuum is measured over time (White, 2012). Pressure or vacuum can be measured directly or by the differential pressure between the test chamber and a reference chamber (White, 2012). The key test parameters include the temperature, the package geometry, the test fixture geometry, the volume of package headspace, the water vapor pressure inside the package, the stabilization time, and the test time (White, 2012).

The Tracer Gas Detection (Vacuum Mode) detects leakage from nonporous, rigid or flexible packages (USP <1207.2>). The test requires the presence of a tracer gas inside the test sample package (USP <1207.2>). Helium is the most commonly used tracer gas but, hydrogen can also be used (USP <1207.2>). The leakage rate of the tracer gas is quantitatively measured using a spectrometric analytical instrument specific for the tracer gas (USP <1207.2>).

To perform the vacuum-mode test, the test samples that have been fully or partially flooded with tracer gas are placed inside an evacuation chamber (USP <1207.2>). The instrument's vacuum pump evacuates the test chamber or fixture, drawing any leaking tracer gas through the analyzer (USP <1207.2>). The absolute leak rate of the test sample may be calculated by normalizing the test results by the partial pressure of the tracer gas within the test sample at the time of test (USP <1207.2>). The test sample leakage is judged acceptable if the absolute leak rate is below that which has been reported to put the product quality at risk (USP <1207.2>).

The Vacuum Decay method is a nondestructive and quantitative assay (USP <1207.2>). It detects leaks in nonporous, rigid or flexible packages. Packages with a porous component can be tested by masking the porous package component (USP <1207.2>). The test sample is placed in a closely fitting evacuation test chamber, which is equipped with an external vacuum source (USP <1207.2>). The test chamber plus test system dead space are evacuated for a predetermined period of time (USP <1207.2>). The targeted vacuum level chosen for the test is predetermined on the basis of the test sample type under evaluation (USP <1207.2>). The rise in dead space pressure (i.e., vacuum decay) is monitored for a predetermined length of time using absolute and/or differential pressure transducers (USP <1207.2>). A pressure increase that exceeds a predetermined pass/fail limit established using negative controls indicates container leakage (USP <1207.2>).

The probabilistic methods include following:

- Microbial Challenge by Immersion
- Tracer Liquid Tests (e.g. Dye Ingress)
- Bubble Tests
- Tracer Gas (Sniffer Mode)

The microbial challenge by immersion and the dye ingress test are the most recognized leak test methods. The update USP <1207> series is encouraging a move toward the deterministic methods.

The microbial challenge by immersion test is suitable for any containerclosure system that can withstand immersion and pressure changes (White, 2012). The test article is immersed in a broth containing the test organism (White, 2012). Brevundimonas diminuta, Serratia marcescens, Escherichia coli and other organisms have been used for this test (White, 2012). The test may be performed in a static mode, where no pressure or vacuum are applied, or in a dynamic, where pressure and vacuum are applied (White, 2012). The purpose of the dynamic mode is typically to simulate air transportation of the product (White, 2012). Key test factors for the assay include the bacterial size and motility, the differential pressure, the challenge media, the exposure time, and the viable count of the microorganism in the challenge media (White, 2012).

The dye leak test is the most common liquid tracer assay (USP <1207.2>). The container is immersed in a methylene blue solution and pressure and vacuum are applied to the container (USP <1207.2>). The containers are inspected visually or via spectrophotometry (preferred method) to observe for traces of blue dye in the container (USP <1207.2>). The key factors for this test include the differential pressure, the compatibility of the dye with the product, the liquid viscosity and surface tension, the training and experience of the inspector (for visual inspection), and the assay sensitivity (for spectrophotometry) (USP <1207.2>). The test is qualitative and destructive (White, 2012).

The bubble test is another probabilistic method. During this assay, the item under test is pressurized to about 3 psig and immersed in a bath containing water or water and surfactant (e.g., polysorbate 80) (USP <1207.2>). This test can detect leaks as small as 10-5 mbar-L/sec (USP <1207.2>). The key test factors include the differential pressure, the test time, the immersion fluid surface tension, the visible inspection conditions (e.g., light intensity, magnification, and background), and the training and experience of the visual inspector (USP <1207.2>). The assay is qualitative and destructive (White, 2012).

During the sniffer mode tracer gas assay, the test samples are flooded completely or partially with the tracer gas via one of several options (White, 2012).

- Piercing a closed test sample to introduce pressurized tracer gas (sealant is applied to close the puncture site) (White, 2012).
- Flooding the test sample before package closure (White, 2012).
- “Soaking” a closed test sample by pressurizing with tracer gas (most applicable to larger leak detection) (White, 2012). The test samples are checked for leakage by scanning the outer package surfaces using a vacuum wand (White, 2012). The use of negative and positive controls along with the test samples provides evidence of test method limit of detection (White, 2012). The sniffer mode is generally chosen when the leak location must be identified (White, 2012).

Method Development

The container closure integrity test needs to show the complete picture of container closure integrity over the lifecycle of the product. This package integrity verification typically occurs during three product life cycle phases. The life cycle phases include the development and validation of the product-package system, the manufacturing site of the product, and the commercial product shelf-life stability assessments.

Any leak test requires optimization for each product-package application (USP <1207.1>). All methods have limitations, but the following aspects should be considered when choosing a suitable method:

- Methods must be suitable for its intended use (Li, 2013)
- Methods must be applicable to the specific drug productpackage (e.g. drug products can interact with CCI defects) (Li, 2013)
- Methods must detect leaks effectively (Li, 2013)
- Non-destructive CCI testing (Li, 2013)

It is recommended to choose a preliminary method following vendor’s recommendations or literature research. The choice of method depends on the specific desired outcomes such as, detecting the presence of leak paths, determining the location of leak paths, measuring the leak rate for the whole package, and evaluating the potential for microbial ingress (USP <1207.1>).

Positive and negative controls need to be created for the assay in order to be compliant with regulations. The controls are designed and assembled with consideration of the container–closure design, the materials of construction, the characteristics of anticipated package leaks, and the impact of product contents on test results (USP <1207.1>). The positive controls are needed to simulate defects in the container closures. However, leaks that occur naturally are rarely uniform holes or channels. They are generally complex tortuous paths (USP <1207.1>). The controls are typically tested alongside the intact samples.

There are many methods are available to create positive controls. Table 1 demonstrates the advantages and disadvantages of the different methods used to create positive controls.

In addition to choosing a preliminary method and creating control samples, the acceptance criteria must be predetermined. The following list of criteria is typical for container closure integrity testing:

Positive Control Type	Advantages	Disadvantages
Micro-pipettes (Li, 2013)	• Easy sample preparation	• Fragile • Broken tips may not be easily detected
Laser drilled holes (Li, 2013)	• Sample geometry can remain unchanged • Better resemble natural defects in glass (cracks) and polymer (pinholes)	• Cost • "Hole" size of laser-drilled effects needs to be calibrated
Microtubes (Li, 2013)	• Easy sample preparation • Robust • Easy to use	• The length of the microtube defects usually longer than that of the typical "real-world" defects
Wire	• Easy to prepare • Easy to use	• Can create a tenting effect where the size of the control is not accurate

- All negative controls must pass (USP <1207.1>).
- All positive controls with leaks at or above the claimed limit of detection must >fail (USP <1207.1>).
- A lower limit of detection must be established (USP <1207.1>).
- An upper limit of detection should be established (USP <1207.1>).
- The percentage of positive controls to be detected must be specified in the validation study protocol by the end user (USP <1207.1>).

USP <1207> and ICH Q2 (R1) describes how to determine and establish a limit of detection (LOD) for the method chosen. The LOD is the smallest leakage rate or leak size that the method can reliably detect, given the product-package of interest (USP <1207.1>). The LOD for a given method is defined as the smallest-leak positive control subset that consistently demonstrates leakage in 100% of the positive-control subset units at that defect size and larger (USP <1207.1>). There are multiple methods available to determine limit of detection criteria.

USP <1207> also describes the need to verify the largest leak detection capability or upper limit of detection. All analytical methods have optimum measurement ranges (USP <1207.1>). When selecting a leak test method, one should also consider the largest leak sizes likely to occur in the sample population (USP <1207.1>).

Once an optimized method is created, multiple lots should be tested representing the package integrity at the extremes of finished product-package profiles (USP <1207.1>). In other words, relevant product variations should be tested, various packaging component sources and lots should be tested, different drug products batches should be tested, and different packaging sites and lines should be tested, if applicable (Li, 2013). The quantities to be tested should be sufficient to provide adequate assurance of the package integrity (USP <1207.1>).

After the method has been chosen, optimized, and qualified, a validation protocol should be written outlining the successful trials and the parameters created during the method develop phase.

Method Validation

Container closure integrity methods need to be validated for the specific drug-product package. Various components, such as the drug product, can affect the testing outcome. The validation of the leak test method is required to demonstrate the test method precision, accuracy, range, robustness, and detection limit (Li, 2013). USP <1207> Validation of Compendial Procedures and ICH Q2(R1) provides good guidance on method validations.

Method accuracy demonstrates the ability of a leak test to correctly identify or size leaks (USP <1207.1>). While, method precision is a measure of the test result reproducibility. Method precision is demonstrated during the method validation by testing a randomly mixed population of negative and positive controls over multiple days by multiple operators and, when possible, using multiple test instruments (USP <1207.1>).

The established validation protocol should be followed when performing the validation. Validations are typically performed in triplicate by performing the method created in the method development phase. The quantities of samples to be tested must be sufficient to provide adequate assurance of package integrity and will likely vary on the basis of:

- The complexity of the product–package (USP <1207.1>).
- The specifics of the user specification requirements (USP <1207.1>
- The prior experience of the producer.(USP <1207.1>).

The method validation protocol should be written to describe introducing a number of defects of known size or leak rate as controls. Acceptance criteria for leak test method validation should include the following:

- All negative controls pass (no leaks are identified) (USP <1207.1>).
- All positive controls with leaks at or above the designated limit of detection fail (leaks are detected) (USP <1207.1>).
- An integral package is one that conforms to specific product-package maximum allowable leakage limits (USP <1207.1>). For some test methods (e.g. liquid tracer leak detection by mass spectrophotometric analysis), test blanks are also included as part of method validation and routine testing (USP <1207.1>). Blanks are not equivalent to, and should not substitute for, negative controls (USP <1207.1>).

After the successful validation of the method, a report should be written describing the acceptable parameters, acceptance criteria, validation results, and the method to be used for routine testing and stability testing. A routine testing SOP (standard operating procedure or test method) should be established. The routine SOP should lock down all the parameters and acceptance criteria for the specific product/ container-closure system so that the test is performed the same way every time. Quantities of samples to be tested must be sufficient to provide adequate assurance of package integrity (USP <1207.1>). “The manufacturer should be able to justify the amount of testing required on the basis of statistical process control results generated during the validation phase, and later, on the basis of routine manufacturing product-quality trending analyses.” (USP <1207.1>).

The container closure integrity should be re-evaluated when changes are required in package design, package materials, or manufacturing/ processing conditions (USP <1207.1>).

Stability Testing

The routine testing SOP should be utilized when performing CCIT for stability testing. Container-closure integrity should be demonstrated as part of the stability program over the shelf life of the product for new and existing products (FDA Compliance Program Guidance Manual, 2015).

Container closure integrity testing may not replace the sterility test for release testing. However, container-closure integrity testing can be used to replace sterility testing in stability protocols (Ewan, S. et al., 2015). The sterility testing or alternatives (e.g. container/closure integrity testing) should be performed minimally at the initial time point and at the end of the proposed shelf-life (ICH Q5C). It is highly recommended to do interim time points in case a time point does not pass specifications. Some companies perform stability testing on a yearly basis until the end of the stability study.

If a non-destructive test has been validated for the specific containerclosure system, it is useful during stability studies. The same container can be used throughout the stability period. This saves money and allows for more meaningful profiles of container-closure integrity (White, 2012).

Bracketing is also a useful strategy in stability studies, when the same strength and exact container/closure system is used for 3 or more fill contents, the manufacturer may elect to place only the smallest and largest container size into the stability program (ICH Q5C). This strategy will save time, money, product, and room in the stability chambers.

Conclusion

Container Closure Integrity Testing evaluates the adequacy of a container closure barrier systems to maintain a sterile barrier. Multiple guidance documents and regulations are available that discuss CCIT. This testing is reviewed by regulators. Understanding the container closure system, the assays, the regulations, and reviewing past observations are excellent ways to establish a compliant method.

Many different methods are available to perform CCIT. The USP <1207> update divides the methods into deterministic and probabilistic categories. There is a move to move toward more deterministic methods. The USP <1207> revised guidance series removes the recommendation to compare CCIT methods to microbial ingress testing and describes several methods that are available for use. Package integrity verification occurs during the development and validation of the product-package system, product manufacturing, and commercial product shelf-life stability assessments (USP <1207.1>). CCIT needs to show container integrity over the life cycle of the product. The methods require optimization for each product-container/closure application. But, all of the methods have their limitations.

During method development, a preliminary method is chosen, optimized, and qualified. Target acceptance criteria and leak testing parameters should be established and optimized (USP <1207.1>). Controls should be created and the quantities of samples for testing should be sufficient to provide adequate assurance of package integrity (USP <1207.1>). After the method has been optimized, the qualification trials should be performed to demonstrate the method is capable of passing validation.

Container closure integrity needs to be validated for each specific drug-product package. Validations are typically performed in triplicate. USP <1207> recommends to randomly mix negative and positive control populations over multiple days, with multiple operators, and if possible, using multiple test instruments. The acceptance criteria should include the following:

- All negative controls pass (no leaks are identified) (USP <1207.1>).

- All positive controls with leaks at or above the designated limit of detection fail (leaks are detected) (USP <1207.1>).
- An integral package is one that conforms to specific product-package maximum allowable leakage limits (USP <1207.1>).
- Upper and lower limits of detection should be established as well as any key testing parameters (USP <1207.1>).
- Routine and stability testing should be performed per an approved standard operating procedure or method. Package integrity should be re-evaluated when changes are required in package design, package materials, or manufacturing/ processing conditions (USP <1207.1>).

Finally, it is important to note that CCIT can be used in place of sterility testing during stability studies. Non-destructive CCIT methods save product and money and bracketing strategies can be utilized during stability studies when appropriate (ICH Q5C). It is recommended to perform stability studies at the initial time point, and then annually until the product shelf life time point is reached.

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Author Biography

Crystal Booth *is an Independent Pharmaceutical Microbiology Consultant for Pharmaceutical Advisors, L.L.C. She earned her Bachleor’s Degree in Biology from Old Dominion University and her Master’s of Microbiology Degree from North Carolina State University. She has 17 years of experience in Pharmaceutical Microbiology.*

Crystal has developed and performed numerous method validations. Some of the methods include Microbial Limits Testing, Bacterial Endotoxins Testing, Particulate Testing, Sterility Testing, Pharmaceutical Water System Validations, Environmental Monitoring Programs, Surface Recovery Validations, Disinfectant Efficacy Studies, Minimum Inhitory Concentration Testing, Anitmicrobial Effectivesness Testing, Hold Time Studies, Container Closure Integrity Testing, and various Equipment Validations (Autoclaves, Isolators, Vitek, Biolog, EM equipment, Conductivity Meters, pH Meters, Pipettes, PTS Unit, Endoscan, TOC equipment, Incubators, etc.).

Crystal has worked in both R&D and Quality Control Laboratories, including a Start-up Company. She has developed and validated methods for Antibiotics, Otics, Topical Creams, Topical Ointments, Oral Solid Dose Products, Oral Liquid Dose Products, Veternary Products, Human Parenterals, Aseptically Filled Products, and Terminally Sterilized Products. She has experience working with global markets and regulatory bodies.