BioPhorum

CONTAINER CLOSURE INTEGRITY

Method validation and misconceptions

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Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum's membership now comprises top leaders and subject matter experts from global biopharmaceutical manufacturers and suppliers, working in both long-established and new Phorums. They articulate the industry's technology roadmap, define the supply partner practices of the future, and develop and adopt best practices in drug substance, fill finish, process development and manufacturing IT.

In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

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Executive summary

Container closure integrity (CCI) testing has evolved from a compliance-driven activity to a strategic quality assurance tool, especially in the context of sterile product manufacturing. As regulatory expectations shift toward deterministic, validated methods, particularly under USP <1207>[1] and ICH Q2(R2)[3], the pharmaceutical industry faces increasing pressure to demonstrate method sensitivity, reproducibility and lifecycle applicability.

This paper, developed by the BioPhorum fill finish/CCI workstream, addresses persistent misconceptions around CCI method validation and offers a harmonized framework for selecting and validating leak detection technologies. It emphasizes the importance of aligning test method capabilities with product risk, container format and regulatory phase, whether clinical or commercial.

Key themes include the role of positive controls, the use of bracketing strategies to streamline validation across formats, and the need to differentiate between probabilistic and deterministic methods. The paper also explores operational challenges such as occlusion, equipment qualification and the limitations of certain technologies like high voltage leak detection (HVLD) and dye ingress.

By integrating scientific rigor with practical feasibility, this document aims to support cross-functional teams in implementing robust, phase-appropriate CCI strategies that meet both regulatory expectations and manufacturing realities.

1.0

Introduction

Container closure integrity (CCI) is a critical quality attribute for sterile pharmaceutical products, ensuring that the container closure system (CCS) maintains sterility, stability and protection throughout the product lifecycle. As regulatory expectations evolve, particularly under USP <1207>[1] and ICH Q2(R2)[3], the industry faces increasing scrutiny over selection, validation and justification of leak detection methods. Despite the availability of advanced technologies, misconceptions persist around what constitutes a validated method, when good scientific practice (GSP) is sufficient and how to interpret performance characteristics such as detection limit, specificity and robustness. This paper was developed to address these gaps and provide a harmonized framework for CCI method validation.

Key performance characteristics such as accuracy, precision, specificity, detection limit, linearity, range and robustness are essential to ensure that the validation methods yield reliable and reproducible data. This paper discusses various validation strategies, including product-specific and bracketed approaches, which test a range of sample parameters to ensure comprehensive validation.

Acceptance criteria are established based on scientific data, industry guidance and regulatory requirements, ensuring that the methods are suitable and capable of providing reliable detection. Positive controls with known defects are integral to method development, validation and routine testing, helping to ensure the reliability of the methods.

This paper distinguishes between clinical and commercial validation, highlighting that clinical validation focuses on ensuring safety during trials with more flexibility, while commercial validation is more stringent and aims to guarantee long-term product safety and efficacy. It also explores the challenges and limitations of different CCI techniques, emphasizing the need for appropriate method selection based on the specific requirements of each presentation.

Techniques discussed include HVLD, helium leak testing, laser head analysis, vacuum decay, CO_2 ingress, qualitative pressure leak test (QPLT) and mass extraction. Each technique has its own set of challenges and limitations; this paper provides practical insights and recommendations to enhance the reliability and effectiveness of leak detection in pharmaceutical packaging.

By addressing these key aspects, the paper aims to provide a comprehensive understanding of CCI method validation, ensuring robust and compliant methods that safeguard the quality and safety of pharmaceutical products.

2.0

When do you need a validated method vs good scientific practice?

In the context of container closure integrity testing (CCIT) methods, GSP requires developing methods that conform to the foundational requirements outlined in USP <1207>[1]. These base requirements specify that the instruments and equipment utilized must be properly qualified, and the method must include a system suitability test to ensure reliability and accuracy.

ICH Q2(R2)[3] and USP <1225>[2] state that method validation is demonstration that the method has an acceptable Measurement System Analysis (MSA) and is suitable for its intended use by meeting predetermined acceptance criteria. In the context of CCIT methods, as specified in USP <1207>[1], method validation demonstrates that a leak test method can meet all relevant leak detection performance criteria specific to the Contamination Control Strategy (CCS). Methods that are validated are considered aligned with good manufacturing practice (GMP).

The recommendations below are for the minimum validation status of methods according to *BioPhorum's Holistic Approach to Container Closure Integrity*[5].

Developmental phase	Minimum method validation status
• Characterization • Process qualification*	Good scientific practice (GSP)
• Design verification • Process validation*/Process performance qualification (PPQ) • Routine manufacturing testing • Transportation/Shipping studies • Clinical studies • Stability testing	Good manufacturing practices (GMP)

* Component assembly process, including machinability or engineering runs to define the manufacturing process[5].

3.0

What needs to go into method validation for CCI?

3.1 Method development and validation criteria

Method validation for CCIT involves demonstrating that a method used to identify leaks for the CCS is fit for use. Validation is preceded by development of the method and qualification of the instrumentation and/or equipment.

3.1.1 Method development

When developing a method for CCI, it is essential to evaluate the type of primary packaging and its contents in relation to the test method. The equipment fixturing, the specialized support and holding apparatus designed to secure the primary packaging during testing, should be tailored specifically to facilitate accurate assessments of the intended packaging.

The effectiveness of a fixture hinges on its design, the materials used in its construction and its dimensions. A well-designed fixture ensures that the packaging is held securely in place, minimizing movement and allowing for precise measurements. During the development phase, critical dimensions must be defined and validated, such as through a first article inspection, to guarantee that the fixture functions properly for its intended purpose.

These considerations should encompass both the design of the fixture and the attributes of the data to be obtained from the selected testing methodology.

3.1.2 Choice of test method

No single CCI methodology is applicable to all CCSs. CCI methods can be divided into several dichotomous categories:

Assessment type

- **Deterministic:** This type of leak test method follows a predictable chain of events, utilizing physicochemical technologies that provide objective quantitative data. Examples of deterministic methods include vacuum decay, pressure decay, mass extraction, helium leak detection, high voltage leak detection, micro-flow liquid or gas detection, laser-based headspace analysis.
- **Probabilistic:** This type of leak method is stochastic in nature, often relying on a series of events with uncertainties that provide qualitative data based on subjective observation of a specific quality, attribute or characteristic of the test sample. Examples of probabilistic methods are dye ingress test, bubble test, microbial ingress test.

Sample impact

- **Destructive:** A destructive method alters the physical or chemical properties of the sample during measurement, making repeated testing on the same sample either impossible or likely to yield varying results
- **Non-destructive:** A non-destructive method allows for measurement without permanently altering the physical or chemical properties of the tested sample. This enables repeated measurements on the same sample, which are expected to produce consistent results. However, if a method is claimed to be non-destructive, it must be demonstrated that it does not impact the product assay or cause degradation of the sample. This includes verifying that the method does not affect product potency, stability or introduce any risk to sterility assurance.

Data output

- **Variable data:** Variable data refers to numerical values measured on a continuous scale with meaningful intervals. In the context of CCIT, quantitative methods generate variable data that can be directly or indirectly correlated with leak presence, leak location or leakage rate.

Key characteristics include:

  - Provides numerical results
  - Objective and reproducible
  - Minimizes human interpretation.

- **Attributive data:** Attributive data classifies outcomes into discrete categories such as pass/fail, conforming/non-conforming or yes/no. These are typically associated with probabilistic methods or visual assessments where outcomes are binary and not measured on a continuous scale.

3.2 Incorporation of system suitability

System suitability is a way of ensuring that the leak test method including all factors, which may be subject to variability, and that may impact test results (such as instrumentation, analysts, test sample preparation steps and test environment) are adequately controlled and maintained in such a fashion that the method is rugged and robust. This may include performing the method with control samples to demonstrate that the method is capable of differentiating non-leaking samples (negative controls) with defective/leaking samples (positive controls).

3.3 Risk assessment activities

Risks to the integrity of the method and collection of data should be assessed. Preventive measures should be implemented to minimize false positives and false negatives. False positives identifying a leak where none exists may result from issues such as faulty sealing gaskets or unintended tracer gas saturation in the test chamber. False negatives occur when actual leaks go undetected.

3.4 Equipment and instrument qualification

All equipment and instrumentation used in method validation activities must be qualified prior to use. This includes evaluation of functionality through installation qualification (IQ), operational qualification (OQ) or performance qualification (PQ) to demonstrate the equipment and instrumentation are fit for purpose. As part of qualification and ongoing use, detection capabilities should be verified using appropriate calibration tools or reference standards that simulate leak test conditions. Additionally, periodic verification of equipment performance should be implemented to ensure continued reliability. This may include the use of positive controls or known defect standards to confirm that the system maintains its sensitivity and accuracy over time.

3.5 Method performance characteristics

The demonstration that a CCI method is fit for use is by meeting relevant leak detection performance criteria. USP <1207.1>[1] offers guidance on the performance criteria for method validation as outlined in ICH Q2(R2)[3] and USP <1225>[2], specifically in relation to CCI methodologies. Not all performance criteria may be applicable to every CCI method, and it is usually possible to design the experimental work such that the appropriate performance characteristics can be considered simultaneously to provide a sound, overall knowledge of the capabilities of the CCI method. Specified per ICH Q2(R2)[3], the minimum performance criteria to be assessed are specificity or accuracy/precision and detection limit/quantitation limit. Acceptance criteria are explained further in the next section.

Guidance on method performance characteristics with respect to CCI is given in USP <1207.1> Section 4. Table 1 below summarizes these performance characteristics along with illustrative examples to support interpretation and application.

Table 1: USP <1207.1> Performance characteristics and illustrative examples

Performance characteristic	Description per USP <1207.1>	Example of characteristic
Accuracy	Qualitative ability to detect leaks above a claimed detection limit or alternatively the quantitative measure to a known leak rate/standard.	• Proportion of non-defective samples identified as 'Pass' and defective samples identified as 'Fail' during method validation • Alignment of method data to a known standard during method validation.
Precision	Demonstration that the method yields data that is repeatable and reproducible.	• Measurement system analysis that incorporates testing across multiple operators, days/rounds and laboratories as applicable during method validation.
Specificity	Ability of the method to accurately identify leaks despite interfering factors that may cause false detection.	• Demonstration that the method is capable of correctly differentiating leaking versus non-leaking samples/standards, such as testing with negative and positive controls • Incorporation of preventative steps and method set up to prevent false results such as issues with fixture sealing or tracer gas saturation.
Detection limit/ Quantitation limit	Smallest leakage rate or leak size that the method can reliably detect. Also known as limit of detection (LoD) or method sensitivity.	• Leaking samples/standards such as positive controls correlate to a predetermined leakage rate/defect size • Demonstration that the method is capable of consistently identifying a given leakage rate or leak size through multiple measurements.
Linearity/Response*,**	Method capability to produce results proportional to leakage rate/defect size.	• The method's capability to produce results that vary in response to leak size, acknowledging that the relationship may not be strictly proportional • Demonstration that the method values change depending on the leak size, while considering influencing factors such as leak position, orientation relative to product level and container geometry.
Range*	Interval between the smallest and largest leak size (or leakage rate) that can be detected.	• Both marginal and gross leaks should be considered to reflect the method's sensitivity and practical application limits • Use of positive controls (known leak sizes) is essential to establish detection capability • Use of negative controls (non-leaking containers) is recommended to confirm absence of false positives, establish baseline noise and support specificity and robustness assessments.
Robustness*	Method resilience to deliberate changes in procedural parameters.	• Incorporating small variations to method test parameters to demonstrate that method data is not impacted.

* Performance characteristics such as linearity/response, range and robustness may be demonstrated during method development using characterization studies.

** Performance characteristic 'linearity' is denoted as 'response' in ICH Q2(R2)[3].

4.0

Method validation and bracketing

4.1 Introduction and benefits

The strategy used to validate a given method may encompass a variety of approaches. These approaches may incorporate the usage of actual samples, reference material and standards to demonstrate the method is fit for use. The foundation of any approach is the provision of appropriate justification to demonstrate the relevance of the tested materials to the intended container closure system (CCS).

A product-specific approach entails a comprehensive study with actual samples from the intended CCS. This approach offers substantial evidence of its applicability to the specific CCS. However, this approach may be constrained if the method is intended to test a variety of sample types, as each new sample type would require a full comprehensive study.

A bracketed approach involves incorporating testing over a range of sample/test parameters that can encompass a variety of sample types. With this approach, the method can be demonstrated to be fit for use over an established range of parameters. Sample types within this range may be considered validated through appropriate justification or by leveraging smaller, truncated studies to demonstrate applicability. This approach might include a comprehensive large-scale study, supported by smaller studies to refine the LoD, specificity and method sensitivity as applicable to the methodology used.

4.2 Considerations when using a bracketing approach

The primary consideration when adopting a bracketing approach is the selection of sample/test parameters that are applicable to the intended CCS. At a minimum, a worst-case selection for the parameters is recommended, to ensure a conservative evaluation of the method and to confirm that the actual use case is less restrictive than the conditions tested during validation.

Example parameters that can be considered for bracketing vary based on the type of CCI methodology and intended CCS, including gas concentration, fill volume or sample viscosity. In the instance of viscosity, a very viscous product may pose the worst-case scenario for pathway/vent obstruction.

By consolidating these methodologies into a validated package, enhanced with a truncated study, the efficiency and cost-effectiveness of leak testing across similar or the same containers with different product stock keeping units (SKUs), can be substantially improved. This structured approach facilitates informed decisions about necessary parameters, avoiding the need to bracket every possible variable. It focuses on those that significantly impact the test, particularly in large-scale applications.

5.0

Acceptance criteria

Acceptance criteria for analytical testing are specific conditions that must be met to ensure a particular test is suitable and capable of providing accurate and correct detection following standard operating procedures (SOPs). These criteria must meet the expectations of user requirements, quality control systems, regulations, industry standards and guidance. They are based on knowledge, experience and scientific data, in addition to industry guidance and regulatory requirements. Acceptance criteria are developed to measure changes in the product during manufacturing, storage and beyond. General acceptance criteria guidance has been stated in USP <1207>[1] and is summarized in Table 1. Each characteristic, such as accuracy, precision, specificity, detection limit, range, robustness and response, is defined in the context of method validation, with example acceptance criteria provided to support consistent and risk-based evaluation. Acceptance criteria may change to fit requirements for a specific product in a special primary packaging system.

Table 2: Summary of CCIT performance characteristics and corresponding acceptance criteria

Performance characteristic	Acceptance criteria	Example of acceptance criteria
Accuracy	Accuracy is defined as the detection rate of truly negative and truly positive results, which can be taken as the percentage of correctly identified negative and positive samples versus all samples in the validation testing.	One hundred per cent accurate means all negative samples pass, all positive samples fail and there is no equivocal sample disposition during the method validation.
Precision	Precision is the demonstration of method repeatability and reproducibility. The acceptable statistical confidence and reliability should be based on sample size and risk.	The repeatability and reproducibility (R&R) of the validation can be analyzed by Gage R&R. Each biomanufacturer is expected to determine a statistical confidence and reliability for the repeatability and reproducibility of their probabilistic methods based on their own risk assessment.
Specificity*	Specificity is defined as the detection rate of truly positive results, which can be calculated as the percentage of correctly identified positive samples versus all known positive samples in the validation testing. The determination of an acceptable percentage should be justified.	Each biomanufacturer is expected to determine a statistical confidence and reliability for the specificity of their probabilistic methods based on their own risk assessment.
Detection limit*	The detection limit of a CCI testing method refers to the smallest defect size or the lowest level of leakage that the method can reliably detect. It is a critical parameter that defines the analytical sensitivity of the testing method and its ability to identify even the smallest breaches in the CCS. The regulatory expectation dictates that the detection limit for commonly used primary packaging systems, such as syringes and vials, should not exceed 20µm. During the packaging qualification phase in development, the detection method must have a detection limit equal to or smaller than the maximum allowable leakage limit (MALL) to ensure United States Pharmacopeia (USP) compliance. However, during routine testing, the detection limit may exceed the MALL, as the focus shifts to identifying larger defects that may arise from manufacturing processes, storage, distribution or end use.	The detection limit for deterministic test methods is expected to be determined as the smallest defect size/ leak rate for a certain package detected 100% of the time. Each biomanufacturer is expected to determine a statistical confidence and reliability for the detection limit of their probabilistic methods based on their own risk assessment. The minimum detection limit to meet for a detection method is correlated with microbial ingress risk comparison study between the leak size and the ingress rate.

* Performance characteristics such as linearity/response, range and robustness may be demonstrated during method development using characterization studies.

** Performance characteristic 'linearity' is denoted as 'response' in ICH Q2(R2)[3].

Table 2: USP <1207.1> Performance characteristics and illustrative examples (continued)

Performance characteristic	Acceptance criteria	Example of acceptance criteria
Range	Leak test method range is the interval between the smallest and largest leak size (or leakage rate) that can be detected by a given leak test method with a suitable level of accuracy and precision. Typically, the lower limit of the range is set as the detection limit while the upper limit could be higher than the widely accepted 20µm defect size. Defining the range is crucial for understanding the method's applicability and ensuring it meets the requirements for detecting potential defects in the CCS.	Test methods are expected to detect gross leaks that are larger than the maximum defect size which is validated by the method. Certain type of defects that intentionally causes significant leakage may be included in method validation to confirm the detection of such gross leaks.
Robustness	Robustness is the method's ability to accurately identify leaking versus non-leaking packages despite small but deliberate variations in procedural parameters, providing an indication of the method's suitability during normal usage. Therefore, the procedural parameters with intrinsic variation require control and need to be monitored and/or recorded.	Robustness in procedural parameters such as incubation time and pressure differential for a dye immersion testing, needs to demonstrate the same sensitivity and specificity, when the incubation time is slightly extended or shortened and/or the pressure fluctuates in a predetermined range.
Response	Ability of the method to produce results that vary in response to leak size, acknowledging that the relationship may not be strictly proportional.	$R^2 \geq 0.95$ where applicable. Method should distinguish between at least three leak sizes with statistically significant differences. Response must be repeatable across replicates. Influencing factors (e.g. leak position, product level) should be considered.

* Performance characteristics such as linearity/response, range and robustness may be demonstrated during method development using characterization studies.

** Performance characteristic 'linearity' is denoted as 'response' in ICH Q2(R2)[3].

Among various performance characteristics, detection limit or the LoD, also known as the analytical sensitivity, is a measure of how well the smallest leak in a defective packaging system can be repeatedly and reproducibly detected by a CCIT instrument or method and differentiated from non-defective ones.

The MALL differs from the detection limit and is typically used during the development stage to qualify a primary container closure for human use. It ensures there is no potential for leaks of specific concern and/or examines the manufacturing process. Concerns can range from highest risk, such as microbial contamination as per USP <1207>, to medium risk like the escape of dosage or entry of foreign matter (medium leak), to low risk, such as air leak into the headspace. MALL is often determined through inherent integrity studies using methods like laser headspace analysis and helium leak detection.

For rigid primary containers, a conservative MALL such as the Kirsch limit of $6x10^{-6}$ mbar·L/sec may be measured with He-leak detection and may be adopted without extensive studies. Meeting the Kirsch limit through inherent CCI testing with defect-free components and a well-controlled assembly process is considered to present negligible to no risk for microbial ingress and product loss, according to USP <1207>. This means well-assembled product packaging is deemed inherently acceptable per USP <382>, before undergoing real-world stresses.

From development through clinical to commercial phases, the BioPhorum holistic strategy paper[5] incorporates established monitors and controls alongside frequent integrity measurements. This approach accumulates knowledge, experience and data regarding product integrity, documented in a living database known as the packaging integrity profile (PIP), as per USP <1207> and PDA Technical Report TR86. The PIP serves as a comprehensive design and process history file, recording historical data and changes for CCI.

The key application of the PIP is to justify the need to avoid using MALL throughout the entire product lifecycle, and instead adopt a risk-based CCI method with less sensitivity to meet phase-specific needs.

For instance, after extensive qualification and validation studies with established controls for packaging design and fill/finish/assembly processes during the development and clinical phases, the commercial phase can utilize the accumulated data to demonstrate that risks have been mitigated. At this stage, the primary concern would be large leaks, and commonly used CCI methods with validated detection limits of <=20um are adequate to ensure the integrity of commercial products.

For new primary container closures with limited prior data on MALL, a validated microbial ingress study can be conducted to establish a practical MALL. This involves testing various controlled leak sizes and assessing the rate of microbial ingress to determine the threshold at which product sterility or integrity may be compromised. While microbial ingress studies can provide valuable insights, they also have inherent strengths and limitations, including variability in microbial challenge conditions and detection sensitivity, which must be considered when interpreting results. Therefore, their use in MALL determination should be scientifically justified and supported by complementary data or risk assessments.

It is important to consider packaging-specific risks, for example, blister packs, which are particularly sensitive to moisture ingress. Even small leaks can lead to significant changes in moisture content, potentially affecting product stability. Additionally, transportation conditions, such as pressure changes and mechanical stress, can exacerbate leak risks and should be factored into MALL determination.

By integrating microbial ingress data with environmental and packaging-specific considerations, a more robust and realistic MALL can be defined, ensuring product protection throughout its lifecycle.

Furthermore, the inherent integrity study for rigid primary container closures can be conducted using empty or placebo-filled CCSs at the early stages, before finalizing the product formulation and qualifying the production line. However, the leak potential identified in this study does not represent the robustness of the fill finish/assembly processes.

5.1 Key considerations for acceptance criteria

5.1.1 Probabilistic versus deterministic methods

After a CCI test method is validated, whether it is probabilistic or deterministic, it is commonly classified as an attribute test with pass/fail as the sole outcome. This can sometimes overshadow the extensive validation effort behind each method. According to USP <1207>[1], probabilistic methods may require larger sample sizes to ensure scientific rigor, whereas deterministic methods, such as vacuum decay, may involve calculating a baseline plus three to six sigma to create a buffer between negative and positive samples. Including a high-level summary of the method in the SOP, along with differentiated acceptance criteria, could be beneficial.

5.1.2 Detection limit versus positive control defect size

The detection limit defines the smallest defect size or leakage rate that a CCIT method can reliably identify. This value must be interpreted within the context of the method's validated operational range, which spans from the minimum detectable defect to the largest defect the method can still characterize without saturation or signal distortion. For deterministic methods, such as helium leak detection or vacuum decay, the lower bound of the range is typically established through repeated detection of calibrated defects (e.g. laser-drilled pinholes), while the upper bound may be defined by gross leak detection capability. It is important to note that the range is not strictly linear, especially for methods where signal response may plateau or be influenced by defect geometry, product viscosity or container orientation. Therefore, method validation should include multiple defect sizes, including those ≤20µm, to confirm consistent sensitivity and to ensure the method can distinguish between marginal and gross leaks with statistical confidence. This aligns with US Food and Drug Administration (FDA) expectations and USP <1207>[1] guidance, which emphasize the use of the appropriately sized positive controls and validated sensitivity thresholds.

5.1.3 Device body, terminus and full package detection

Method validation determines the specific locations on the device that are qualified for leak detection. Given the differences between breaches and gaps as leak pathways, as well as the variations in container components (e.g. syringe stopper, device body, rigid needle shield (RNS)/ septum or tip cap), a worst-case scenario approach may be necessary during validation. For instance, validating a method using laser-drilled defects on the syringe glass barrel might not ensure detection of leaks at the stopper or RNS interface if full-package detection is claimed in the SOP. This is especially relevant for dye ingress methods, where the entire device is submerged in dye, potentially giving the false impression that all such methods automatically qualify for full-package integrity testing.

5.1.4 Sample size versus failure rate determination

Throughout the lifecycle of a product, from development to clinical, commercial and beyond, different sample sizes may be used for various CCIT protocols, including design verification, container closure operational qualification (CCOQ) testing, PPQ testing, is in-process control (IPC) testing, lot release and stability testing. CCI tests are often treated as attribute tests with pass/fail outcomes, which may underestimate the significance of individual acceptance criteria. To address this, the acceptance criteria section in the SOP should specify requirements for each characteristic, including sample size, failure rate allowance and statistical justification. The sample size should be risk based and supported by scientific data, ensuring statistical significance. Larger sample sizes generally require higher minimum detection rates to maintain rigor.

5.1.5 Retest justification

Whether a failed test sample can be retested has been debated for decades. For destructive methods, retesting is not feasible, as the original integrity of the sample is compromised during testing. For non-destructive methods, retesting can be performed if justified scientifically and outlined in the SOP. However, it is important to consider that procedures involving active pressure differentials may alter the seal tightness of the interface; this is particularly true for closures like syringe stoppers that are not locked in place during initial testing.

6.0

Positive controls

A positive control is a package (e.g. vial/syringe/cartridge) with a known defect which breaches the CCI. Positive controls should use the same components and process as those of the package under test, where possible. Positive controls are used during CCI/CCIT method development, method validation, and can be used during routine testing (i.e. system suitability checks).

For method validation, positive controls are used to confirm the LoD of the CCIT method. For deterministic processes, LoD can be shown by processing positive controls with known leak rates on the developed testing equipment with the lowest detected becoming the LoD.

USP chapter <1207>[1] describes positive controls as "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".

6.1 Types of positive control

Table 3: Types of positive control

Defect name	Description
Type/Genuine defect	Although rare within a pharmaceutical manufacturing area, genuine defects are found. They have a place within method validation of CCIT, as they can be taken and used to provide an understanding of the capability of a process for 'real defects' in conjunction with more robust solutions with known leak rates, for example laser-drilled units. Genuine defects are known as 'type defects' in USP <1207>[1]. USP chapter <1207>[1] describes type defects as "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."

Figure 1: Left, a vial with a crimping defect in the cap. Middle, a vial with a crack in the glass. Right, a cartridge with a deformed cap. Samples with these defects manufactured for CCIT specifically.

Table 3: Types of positive control (continued)

Defect name	Description
Laser drilling	Laser drilling refers to the process of using lasers to create precise leaks in CCSs made of various materials (glass, polymer, metal). Originally, the process consisted of mechanically drilling a pilot hole through the main part of the wall of the CCS. The final breakthrough to the inside of the container through a thin remaining part of the wall is achieved by using a laser. The result is usually a cone-shaped opening with a pinhole in the inward-facing part of the container wall. More modern laser-drilling methods use pulsed lasers that open the container wall in a narrower cone shape with a pinhole without mechanical pre-drilling. With the increasing realization that pinholes are rarely the result of genuine packaging defects and that microcracks are a better representation of reality, further laser-drilling processes have been developed for glass containers. These processes use lasers to create melt zones with surrounding microcracks or a network of microcracks. Depending on the manufacturer and the CCS material, the term 'laser drilling' covers a variety of specific defect geometries. The defects produced are flow calibrated in accordance with USP <1207>[1] or certified by microscopic evaluation. As the laser-drilled defect can be located across most of the unit, it gives great control over the creation of consistent development and validation test kits, e.g. for vials, laser-drilled defects can be created in the upper body, mid-body, lower body and base. Laser drilling allows the creation of leaks from approximately 1–2µm. This allows for test kits to be created with varying leak path sizes, e.g. 2µm, 4µm, 6µm, 8µm, etc. to better understand the LoD.
Mechanical/ Thermal shock	Cracks can be manually created in units to mirror genuine rejects. The benefits of using a manually cracked unit are that they are relatively simple to create and mimic a genuine leak path/tortuous path. However, with this type of defect there are inherent issues which are also found with genuine defects, namely that they are extremely fragile so are frequently destroyed when they are processed through equipment.

Figure 2: Vial and a syringe both showing a laser-drilled hole

Figure 3: A thermal-shocked vial

Table 3: Types of positive control (continued)

Defect name	Description
Capillary	A capillary is a tube which is introduced to the sample such that only the inner diameter functions as the sample breach, with the inner diameter being the value used to calculate the leak rate of the unit. However, the effective flow diameter of a capillary microtube may also depend on the length of microtube, where a centimeter longer may decrease the leak size more than 50% based on capillary dimensions and applying the Hagen-Poiseuille equation. Capillary microtubes come in a variety of diameters that correlate to defect size (e.g. 2µm to 20µm). Capillaries can either be added to the unit by manual insertion through an elastomer (such as vial stopper or prefilled syringe (PFS)/plunger) or through the body of the sample. Epoxy sealing around the area of tubing which contacts the stopper or glass wall should be considered to restrict the leakage so that the only leak path is through the tubing.
Microcrack	A microcrack is a real defect on a packaging component, typically on glass, that can be invisible during visual inspection but detectable by the CCI method of choice. This kind of crack can be included in method validation to demonstrate the detection capability of a method. However, this precise control is not essential because naturally occurring defects cannot be reliably controlled and do not provide definitive leak size and morphology characteristics.
Dummies	Dummy units are engineered to replicate the signal response of a genuine defect, while offering greater robustness and safety. These are primarily used for system suitability testing, routine performance checks and program development, rather than for formal method validation, which requires the use of positive controls with known, quantifiable defects. For example, in HVLD, a ceramic vial with a metal core and a drilled micro-hole can simulate a leak response without the risks associated with cracked containers or genuine product use. This facilitates safe and repeatable daily challenge testing. In vacuum leak detection, needle valve assemblies are used to introduce controlled airflow, simulating a leak. When paired with a dummy unit (which acts as a negative control), this set-up mimics a positive control scenario for equipment verification. These assemblies can be calibrated to specific leak sizes (e.g. 10µm), supporting consistent system checks. While dummy units are not suitable for establishing method sensitivity or specificity in a formal validation context, they play a critical role in ensuring equipment readiness, operator confidence and routine system integrity.

Figure 4: A cartridge showing a capillary microtube inserted through the cap elastomer

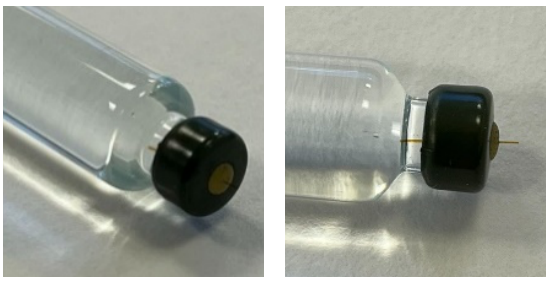


Figure 5: Diagram of a polymicro nano-capillary tubing

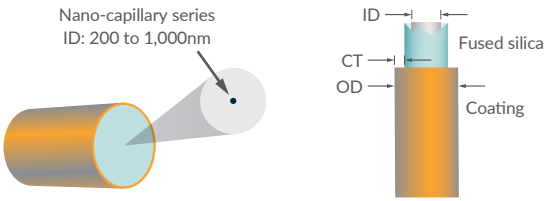


Figure 6: Microcrack on the packaging component

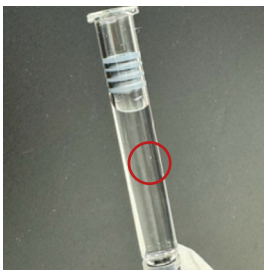


Figure 7: A dummy unit used in conjunction with a vacuum leak detection needle valve

Table 3: Types of positive control (continued)

Defect name	Description
Micropipettes	Micropipettes, like capillaries, can either be added to the unit by manual insertion through an elastomer (such as vial stopper or PFS plunger) or through the body of the sample. Epoxy sealing around the area of the tubing which contacts the stopper or glass wall should be used to restrict the leakage so that the only leak path is through the tubing. Glass micropipettes come with different tip diameters that correlate to defect size (e.g. ≤20µm).
Metal wire	This defect type mimics a leak path typically caused by a hair, fiber or other debris.

Figure 8: A glass tube with the tip pulled into a calibrated micron size capillary

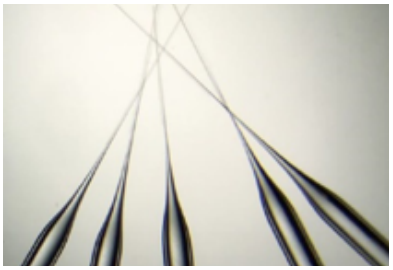
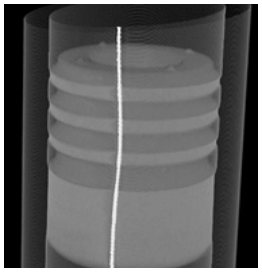


Figure 9: A thin wire placed between the stopper and the vial mouth, underneath the crimped surface to generate a leak path



6.2 Leak path/Hole size

The rate of leakage from a unit can be assessed using techniques such as helium leak testing, where the exact leak rate can be determined. The orifice size can be assigned based on the leak rate, as detailed in USP <1207.1>[1]. The orifice leak size taken from USP <1207.1>[1] assumes that there is a negligible leak path (essentially zero).

In addition, hole size can be measured using microscopy. This gives an understanding of the leak size of the defect, while allowing the measurement to be performed 'in house'. It is important to be aware of the difference between real defect hole size and the calibrated hole size based on airflow rate, when the leak pathway is tortuous and lengthy. For laser-drilled holes, the calibrated hole size may be smaller than the physical dimension measured at the outer surface, unless measurements are taken at the inner surface, which is assumed to be the limiting factor. To achieve accurate inner surface measurements, additional samples are required, not only to build confidence in the laser-drilling process, but also to enable destructive microscopic analysis.

6.3 Occlusion

Occlusion is a shrinking or blockage of a leak path caused by the liquid present in the package, predominantly where the product has flowed through the leak path and then dried on contact with air. The process of occlusion can take minutes or months, dependent on the product. It should be noted that some products do not readily occlude, e.g. water for injection (WFI). It can either manifest as a single 'plug', where the unit would become blocked, or by product lining the leak path where it would reduce the size, possibly below the LoD of the CCIT.

Occlusion poses a quality risk as a unit could have microbial ingress but occlude before it is inspected by CCIT, where it would not be detected. There is potential for clogging defects which can create false negatives. For this reason, it is recommended that occlusion studies are performed to assess the occlusion potential of each product, where deemed necessary.

For method validation, the impact is that known positive controls can change their leak rate over time, with some becoming essentially negative controls once occlusion

becomes total. Control devices should be verified before use, either by referencing previous validation studies or conducting active laboratory validation.

Additionally, laser-drilled defects created with traditional technology may be fragile and prone to cracking or collapsing after the first test, causing occlusion. Use of fresh laser drill defect controls within expiry is recommended. Even with certification, clogging of laser drill defects may still occur during storage and use. A good practice would be to verify selected control samples before critical method validation or GMP testing.

Figure 10: An occluded crack in a vial which has formed a plug on the outside of the unit

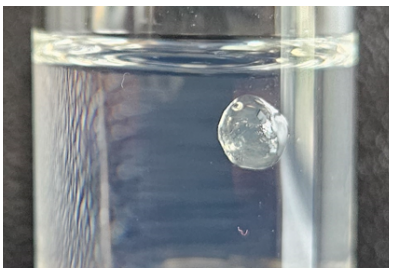


Table 4: Validation format challenges—USP guidance requirements versus practical implementation

USP <1207> guidance	What is practically achievable
Negative controls should represent optimally assembled components	Since the assembly of the test product may still be in the optimization phase during development of the leak test method, educated considerations about the final optimization parameters are often required to create negative controls. For example, deciding an appropriate crimping force for vials or considering the stoppering method and headspace for syringes and cartridges. The alternative case is when the test product's parameters have already been defined so the site developing the method can leverage those parameters directly. Ideally, the same assembly equipment can be used at the site developing the leak method to create the negative controls. However, due to laboratory constraints, this is not always feasible. As a result, each aspect of the fill-and-finish process, as stated as an example above, should be carefully evaluated to replicate or best approximate the optimized process. Whenever possible, it is preferable to develop a leak method using the actual test product, as this minimizes the need to account for formulation-specific considerations (assuming product-specific over platform approach). A common misunderstanding, however, is assuming that the test product can be used directly as a negative control, without change. While the optimized assembly process should maintain product integrity, this does not guarantee the product is entirely free from defects, particularly after shipping. Additionally, using a test product as a negative control would be counterintuitive if the leak test method itself is intended to qualify the fill-and-finish process.
Positive controls should duplicate negative controls	When creating negative controls, factors such as materials of construction, package assembly and component processing should be carefully considered. If these aspects have been thoroughly addressed in the method for creating negative controls, the simplest way to create positive controls is to follow the same process but utilize laser-drilled containers. Positive controls made using alternative defects, such as capillary tubes or micro-capillaries, present additional challenges. As outlined in Section 6.1 on types of positive controls, there are two common methods for inserting capillaries into a container: routing them directly through the stopper or positioning them between the container wall and stopper, followed by epoxy sealing. The advantage of this approach is that the test product within its container can be received directly from the line and have the capillary tube directly inserted into it, so the most representative sample is being used. Unfortunately, the execution is not always as straightforward as it seems and is often difficult to achieve consistently. Also note, the 'duplicate' negative control in this case would use the test product filled container directly from the line, which is not guaranteed to be defect-free. When justifying the replication of representative samples, it is essential to weigh these trade-offs as USP <1207>[1] recommends that positive controls should duplicate negative controls based on the assumption that negative controls mimic the test product as closely as possible. Capillaries pose significant challenges when used in stoppered containers with low break-loose forces (e.g. syringes), as the stopper may shift during insertion, making the sample less representative. An alternative is to insert the capillary between the container wall and the stopper, but this approach comes with often-overlooked complications. During vacuum or pressure cycles, the stopper can still move, resulting in two potential issues: (1) the effective flow diameter may not be maintained as a secondary leak path (epoxy seal breaks from stopper movement) could be created, or (2) the stopper is sealed and held stationary during exposure to pressure conditions, so does not accurately represent test samples, as the stoppers in the test group are expected to shift under such conditions.

7.0

Commercial versus clinical

Table 5 outlines key performance characteristics relevant to the validation of CCI test methods. It is intended to guide the assessment of method capability during the validation for product from development through to commercial, ensuring that the selected method is suitable for its intended use in detecting container closure defects. This framework does not address routine testing or ongoing monitoring but focuses solely on the validation activities required to establish method suitability. Supply chains are global and increasingly complex, and collaboration across the supply chain is necessary if any company is to effectively map their supply chain from raw materials source to the finished good. Supply chain management (SCM) is a resource-intensive undertaking that requires commitment, clarity on priorities and need, and a willingness to invest before starting the SCM journey.

Table 5: Commercial versus clinical products

Method validation for	Clinical products	Commercial products
Objective	To ensure that the CCS adequately protects the product, preventing contamination or degradation during storage and handling. It aims to meet safety standards but is often more flexible in approach. Refer to Section 2.0 for more information.	Ensure robust protection throughout the product's lifecycle. Validation must meet stringent regulatory and quality standards to ensure safety, efficacy and shelf life.
Regulatory requirements	While clinical validation must adhere to regulatory guidelines (e.g. FDA, European Medicines Agency (EMA)), it allows for more flexibility. The focus is on ensuring patient safety, including demonstrating stability over the full shelf life. Methods may be exploratory and use platform or bracketing approaches. There is no formal distinction between short- and long-term stability, stability must be shown for the entire intended shelf life.	Must comply with detailed regulatory standards and GMP. Validation must demonstrate CCI over the full lifecycle. Prior clinical data and risk assessments may reduce redundant testing.
Method rigor and complexity	CCI methods may be more complex and time-consuming due to the need to explore multiple variables and container types. A platform-based approach is often used to reduce testing burden across similar products. Sample sizes may be limited, and reduced approaches may be acceptable based on risk.	CCI methods are typically more streamlined, with fixed parameters and fewer variables. Validation is often simpler due to prior knowledge from clinical development. While deterministic methods are preferred, they are not mandatory. Method selection also considers site resources, timelines and budget. FDA guidance for new drug applications (NDAs) and biologics license applications (BLAs) recommends CCIT methods capable of detecting defects ≤20µm. This benchmark is widely accepted for microbial ingress risk and typically achievable with deterministic methods.
Scope testing	Batch size: Testing typically focuses on smaller batches of products. The goal is to demonstrate that the CCS is suitable for clinical batches and patient safety.	Commercial validation must address full-scale manufacturing. This may involve testing large batches, ensuring that the system is scalable, reproducible and effective in commercial production environments.
Long-term stability	Stability testing during clinical development focuses on short-term data to support trial duration. Long-term data, essential for commercial approval, is typically not required at this stage.	If not already performed for late-phase clinical batches, extensive stability testing is required to ensure that the CCS maintains integrity over the product's entire shelf life from the final product.

Table 5: Commercial versus clinical products (continued)

Method validation for	Clinical products	Commercial products
Documentation and validation reports	The documentation requirements may be less detailed. Companies need to show that the system works for clinical purposes, but full-scale validation reports might not be necessary. The level of documentation may increase over the different clinical phases.	Detailed and comprehensive validation reports are required, including full method validation according to regulatory guidelines (e.g. ICH Q5C, ICH Q2R2). This includes data on precision, sensitivity, specificity, reproducibility and robustness.
Risk tolerance	The tolerance for risk may be slightly higher, as the product is still under investigation. If issues arise, they can be addressed before commercial release.	The risk tolerance is much lower. Any failure in CCI in the commercial phase could lead to recalls, product shortages or patient harm.

In summary, clinical CCIT validation is more focused on ensuring safety during the trial phase with more flexibility, while commercial CCIT validation is stringent, regulatory-driven and designed to ensure long-term product safety and efficacy throughout its market lifecycle.

7.1 Challenges and limitations of test technologies

Not all CCIT techniques are suitable for every product presentation. A thorough understanding of each method's strength and limitations is essential for selecting the most appropriate approach. In an organization, accumulated experience can guide the standardization of specific equipment or testing methods for presentations. However, for those without this internal knowledge, for example teams working with new product types or transitioning to unfamiliar CCSs, a foundational overview becomes especially valuable.

7.2 Understanding methodological limitations

Methodological limitations in CCIT are not always apparent during initial method selection. Real-world variables and product-specific factors influence the performance and reliability of different test technologies.

7.2.1 Sensitivity and specificity

Sensitivity is influenced by multiple factors such as product formulation, container geometry and environmental conditions. Conductive liquids may be compatible with HVLD, while viscous suspensions may obstruct leak paths in vacuum decay. Complex formats like syringes may introduce blind spots, and temperature or humidity can affect detection thresholds. Each application must be evaluated independently.

7.2.2 Applicability across formats

No single method is universally applicable. HVLD is effective for rigid containers but unsuitable for flexible formats. Dye ingress may be limited by container opacity or analyst variability. Laser-based headspace analysis depends on headspace gas composition and fill volume. Feasibility studies are essential to determine suitability methods.

7.2.3 Quantitative versus qualitative output

Binary methods like dye ingress provide pass/fail results, while quantitative methods such as pressure decay may not reliably estimate leak size. HVLD signal strength does not scale linearly with defect size, and laser-based methods lack standardized leak correlation. This limits ability to define acceptance criteria based on leak size or microbial ingress thresholds.

7.2.4 Response and range

Response is not inherent to all technologies. Vacuum decay may demonstrate a correlation between measurement and defect size under controlled conditions, while HVLD and dye ingress typically do not. Response studies can enhance method robustness but should be applied only where appropriate.

7.2.5 False positives and false negatives

All methods are susceptible to false results. False positives may arise from environmental noise or container variability. False negatives can result from clogged leak paths or inadequate detection thresholds. Mitigation strategies include system suitability checks, operator training and complementary testing.

7.3 Risk-based decision framework for method selection

Decision-making in CCI method selection involves navigating uncertainty and balancing competing priorities. A risk-based framework can guide through complex choices and ensure alignment with product and process needs.

7.3.1 Define intended use

Determine whether the method is for development, release or stability testing. Consider the clinical or commercial setting and required sensitivity.

7.3.2 Assess product and container characteristics

Evaluate viscosity, conductivity, fill volume, geometry, material and headspace. Identify interference factors such as stopper movement or crimping defects.

7.3.3 Evaluate method capabilities and limitations

Review published data and internal experience. Consult USP <1207>[1], PDA TR 27[6] and ASTM F2338-24[7], F3287-17[8], F2391-22[9] and F3169-16[10]. Validate under real-world conditions and avoid overreliance on vendor claims.

7.3.4 Consider lifecycle and transferability

Assess whether the method will be transferred between sites or scaled commercially. Document robustness and variability across platforms.

7.3.5 Justify and document decisions

Use risk assessments to support method selection. Define system suitability and validation boundaries. Prepare to explain rationale during audits or regulatory reviews.

7.4 Operational and regulatory considerations

Operational realities and regulatory expectations frequently shape the implementation of CCIT strategies. The nuances of training, compliance and audit preparedness can influence method success.

7.4.1 Operator training and troubleshooting

Training should address method-specific limitations, detection thresholds and troubleshooting strategies. Understanding leak location may aid root cause analysis but is not always essential for batch-level decisions.

7.4.2 Regulatory expectations

Regulators expect a clear understanding of method capabilities and limitations. USP <1207>[1] provides high-level guidance. Risk-based approaches are accepted but must be well justified.

7.4.3 Technology evolution and strategic planning

As CCI technologies continue to evolve, strategic planning becomes critical to ensure long-term applicability and scalability. This section reflects on the dynamic nature of test methods and the importance of forward-looking validation approaches. Method selection should be adaptable to future advancements.

7.4.4 Holistic testing strategies

No single method addresses all risks. Use complementary methods, visual inspection and procedural checks for gross defects. Focus on detecting subtle, high-risk defects.

7.4.5 Gross leak detection and visual thresholds

Gross leaks may be missed due to test limitations. Define and confirm visual inspection thresholds. CCI methods should target non-visible, high-risk defects.

7.5 Recommendations

CCIT technologies offer diverse capabilities, but each has limitations. A contextual, risk-based approach is essential for effective method selection and validation.

Key recommendations:

- Conduct feasibility assessments early in development
- Use complementary methods where appropriate
- Document known limitations and mitigation strategies
- Engage with regulatory guidance as a framework, not a prescription
- Align method selection with product risk, lifecycle stage and operational feasibility.

8.0

Conclusion

This paper presents a comprehensive framework for CCI method validation, developed by the BioPhorum fill finish/ CCI workstream. It addresses common misconceptions and provides practical guidance for selecting, validating and applying CCI methods across the product lifecycle, from development through to commercial manufacturing.

The paper begins by clarifying when full method validation is required versus when GSP is sufficient, based on the phase of development and regulatory expectations. It then outlines the essential components of method validation, including system suitability, risk assessment, equipment qualification and performance characteristics such as accuracy, precision, specificity, detection limit, response, range and robustness.

A key focus is placed on bracketing strategies, which allow validation across a range of container types or product presentations, improving efficiency without compromising rigor. The paper also explores the role of positive controls, detailing various defect types and their relevance to method sensitivity and reliability.

Differences between clinical and commercial validation are highlighted, emphasizing the greater flexibility in early phases and the increased regulatory scrutiny in commercial settings. The document stresses that while deterministic methods are preferred for their objectivity and reproducibility, probabilistic methods may still be appropriate if properly justified.

A detailed comparison of CCI technologies is provided, outlining the strengths and limitations of methods such as helium leak detection, vacuum decay, HVLD, dye ingress and mass extraction. The paper advocates for a risk-based, lifecycle-driven approach, encouraging alignment with USP <1207>[1], ICH Q2(R2)[3] and industry best practices.

Ultimately, the paper underscores that no single method fits all applications. Instead, successful CCI validation depends on tailoring the strategy to the product, packaging system and intended use, balancing scientific rigor with operational feasibility.

Appendix

Recommended minimum method validation characteristics to be validated for probabilistic and deterministic methods with respect to USP <1207.1> Section 4 and ICH Q2(R2):

Method	Performance characteristics	Reference
Probabilistic/Qualitative data (e.g. dye ingress)	• Specificity • Detection limit	USP <1207>[1] ICH Q2(R2)[3]
Deterministic/Quantitative data (e.g. HSA-O2)	• Specificity • Precision • Accuracy • Detection limit	USP <1207>[1] ISO 5725-1[11]

Example study design	Probabilistic example: Dye ingress	Deterministic example: Helium leak detection
Study 1: Multiple operators testing sample set comprising of non-defective and defective samples	Specificity: Due to analysts' assessment of pass/fail Accuracy: Defective samples are detected as leaks Precision: Multiple operators execute test	Specificity: Assessment of pass/fail due to numerical value Accuracy: Defective samples are detected as leaks based on the numerical outcome which is compared to a true gas standard Precision: Multiple operators execute test
Study 2: One analyst tests a set of samples with varying defect sizes (e.g. 5µm, 10µm, 20µm)	Detection limit: Smallest defect consistently detected	Detection limit: Smallest defect consistently detected Response: Signal changes with increase in defect size Range: Range of defect sizes tested
Study 3: One analyst tests positive and negative controls with slightly different equipment parameters	Robustness: Varied equipment settings have no impact on results	Robustness: Varied equipment settings have no impact on results
Not applicable	Response, range	–

Glossary

Term	Definition
Variable data	Data that can be measured on a continuous scale and has numerical values with meaningful intervals.
Attributive data	Data that classifies items into categories (pass/fail, yes/no, conforming/non-conforming).
Container closure operational qualification (CCOQ)	Container closure operational qualification (CCOQ) refers to a specific phase within the validation lifecycle of a container closure system (CCS) used in pharmaceutical or medical device manufacturing. While the term 'CCOQ' itself is not universally standardized across all regulatory documents, it is typically understood as the operational qualification (OQ) stage applied to CCSs.
Deterministic leak test method	A method 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.
Probabilistic leak test method	A method which is stochastic in nature. Probabilistic tests rely on a series of sequential and/or simultaneous events, each associated with random outcomes described by probability distributions. This means 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.
Accuracy	The qualitative ability to detect leaks above a claimed detection limit or the quantitative measure to a known leak rate/standard.
Precision	The demonstration that the method yields data that is repeatable and reproducible.
PFS	Pre-filled syringe.
Specificity	The ability of the method to accurately identify leaks despite interfering factors that may cause false detection.
Detection limit/quantitation limit/Limit of detection (LoD) or method sensitivity	The smallest leakage rate or leak size that the method can reliably detect, also known as limit of detection or method sensitivity.
Linearity/response	The method's capability to produce results proportional to leakage rate/defect size.
Range	The interval between the smallest and largest leak size (or leakage rate) that can be detected.
Robustness	The method's resilience to deliberate changes in procedural parameters.
R&R	Repeatability and reproducibility.
RNS	Rigid needle shield.

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