Container Closure Integrity Testing (CCIT)

Ensuring Integrity, Compliance, and Safety

White Paper

Executive Summary

Ensuring the integrity of container closure systems (CCS) is a critical component of sterility assurance for parenteral products. Compromised CCS can lead to microbial ingress, contamination, and significant patient safety risks, with past incidents resulting in product recalls and, in severe cases, widespread harm. Container Closure Integrity Testing (CCIT) plays a pivotal role in mitigating these risks, ensuring compliance with regulatory standards and safeguarding patient safety throughout a product's lifecycle.

This white paper delves into regulatory requirements, modern CCIT methodologies, and practical strategies for selecting, validating, and optimizing testing methods. These insights are designed to help drug developers ensure product integrity, meet compliance standards, and uphold the highest levels of patient safety.

Beyond the Seal

Container Closure Integrity Testing (CCIT) ensures drug products maintain their sterility throughout their shelf life, which is a critical quality attribute (CQA) for parenteral products. The assurance of Container Closure System (CCS) integrity is fundamental to protect against microbial ingress, contamination, and to ensure patient safety. Incidents in the past involving compromised CCSs have demonstrated the severity of consequences, including widespread infections and fatalities.[1,3] Since 2008, CCI is an accepted method to show sterility.

Over the past few years, multiple recalls have highlighted ongoing concerns with sterility assurance and container closure integrity (CCI), underscoring the need for proactive quality control measures to mitigate the risk of compromised packaging integrity.

Feb. 2017	Sep. 2017	Feb. 2018	Mar. 2021	Mar. 2021	Nov. 2021
Edex® (alprostadil)	**Activase® (alteplase)**	**Labetalol Hydrochloride**	**Phenylephrine Hydrochloride**	**BioNTech Covid Vaccine**	**Levetiracetam**
Endo Pharmaceuticals recalled one lot due to a defect in crimp caps.	Genentech recalled three lots due to potential cracks or chips on vials.	Hospira, Inc. (a Pfizer company) recalled three lots after discovering cracks on the vial rim.	Sagent Pharmaceuticals recalled three lots following a complaint about potentially loose crimped vial overseals.	Authorities in Hong Kong and Macao suspended a batch of the vaccine due to concerns over loose vial caps.	Sagent Pharmaceuticals issued a voluntary recall of four lots due to lack of CCI, with reserve sample vials.

Regulatory Expectations

United States Pharmacopeia (USP) <1207>

USP <1207> provides comprehensive guidance on package integrity evaluation for sterile products. It emphasizes that the selection of appropriate CCIT methods should be based on the specific attributes of the container and product. The chapter advocates for deterministic methods due to their quantitative nature and higher reliability compared to probabilistic methods. It also outlines the validation requirements, ensuring that chosen methods are suitable for their intended purpose and capable of detecting leaks that may compromise product sterility.

European Union Good Manufacturing Practice (EU GMP) Annex 1

The EU GMP Annex 1 outlines the manufacture of sterile medicinal products, including the requirements for container closure systems. The revised Annex 1 emphasizes the need for validated CCIT methods and highlights that visual inspection alone is insufficient to ensure container integrity. It also stresses the application of Quality Risk Management (QRM) principles in determining the frequency and extent of CCIT, encouraging a science-based approach to ensure patient safety.

Parenteral Drug Association (PDA) Technical Report 27

PDA Technical Report 27 offers guidance on the validation and implementation of CCIT methods. It discusses various testing technologies, their applications, and considerations for method selection. The report supports the use of deterministic methods and provides insights into establishing robust CCIT programs that align with regulatory expectations.

International Council for Harmonisation (ICH) Guidelines

ICH guidelines, specifically Q5C, address the stability testing of biotechnological products. They recommend that sterility testing or alternatives, such as CCIT, be performed at the beginning and end of the proposed shelf life to ensure product integrity. This aligns with the emphasis on maintaining container closure integrity throughout the product's lifecycle.

Best Practices for Method Validation and System Suitability

Validating a CCIT (Container Closure Integrity Testing) method requires a systematic approach to ensure its suitability for the intended purpose. The process begins by defining acceptance criteria based on end-user requirements and the specific characteristics of the product and its container closure system. For example, leak detection thresholds should align with the product's critical quality attributes, such as sterility and moisture control. Key validation activities include:

- **Sensitivity Testing:** Verifying the method's ability to detect small leaks by using artificial leaks of known size.
- **Reproducibility:** Ensuring the method consistently delivers accurate results across multiple runs and operators.
- **Robustness Assessment:** Evaluating the method's performance under varying conditions, such as changes in environmental factors or sample preparation techniques.

Regulatory bodies like USP and EMA emphasize the importance of system suitability testing (SST), which involves using positive and negative controls to confirm that the testing setup is functioning correctly and producing reliable results for each session.
Comprehensive documentation is essential for regulatory compliance and smooth audits. This includes detailed protocols, validation reports, and standard operating procedures (SOPs) to demonstrate adherence to established standards.

Methods for CCIT

Traditionally, container closure integrity was established using so called probabilistic methods, such as dye ingress or microbial ingress tests. These methods are based on probabilistic outcomes and operator skill, making them qualitative assessments with inherent uncertainties, requiring larger sample sizes, long wait for the result in case of microbial ingress tests (mibi) tests, and often provide less consistent results.[1,3] Deterministic methods, such as vacuum decay, helium leak detection and laser-based headspace analysis rely on physicochemical measurements, making them fast, objective, sensitive and quantifiable and independent from individual operator assessments.[1,3] With deterministic testing, trends can be followed over time, which is not possible for probabilistic pass/fail results.

The regulatory landscape for CCIT has evolved, emphasizing deterministic over probabilistic methods. The revised United States Pharmacopeia (USP) <1207> chapter reflects this shift, advocating for deterministic methods due to their higher reliability and quantitative output.[1,3] This regulatory preference is driven by the higher accuracy, repeatability, and sensitivity offered by deterministic methods, which align with Quality by Design (QbD) principles to build quality into the product lifecycle from development to post-market.[2,3]

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Overview of CCIT Methods

There are a variety of suitable options for CCIT methods, each with advantages and limitations. When choosing the appropriate testing method, factors such as the type of container closure system (e.g., vial, syringe, or flexible packaging), the product's physical and chemical properties (e.g., liquid or lyophilized form, gas headspace), the required sensitivity level, and regulatory expectations must be considered. Additional elements such as cost, throughput, non-destructive testing requirements, and sample availability also play a significant role. The table below provides an overview oft the most widely employed methods, advantages, disadvantages, and use cases.

	He Leak	Laser-Based Headspace Analysis	Vacuum / Pressure Decay	Microbial Ingress	Dye Ingress
Description	Measures helium escaping from a CCS using a mass spectrometer for high sensitivity leak detection.	Uses a laser to measure changes in gas composition (e.g., oxygen) within the headspace of a container.	Detects leaks by measuring pressure change in a sealed chamber after a vacuum or pressure is applied.	Tests the CCS's ability to prevent microbial contamination by exposing it to bacteria under controlled conditions.	Exposes the CCS to a dye under vacuum/pressure; ingress is inspected visually for indication of leaks.
Advantages	Extremely high sensitivity; quantitative; reliable for small leak detection.	Non-destructive; quantitative; suitable for long-term stability monitoring and gas ingress; can be used under cooled environment (e.g. storage conditions).	Non-destructive; automated; suitable for routine testing; good for medium sensitivity applications.	Directly mimics real-world contamination risks; comprehensive for sterility assurance.	Simple; low cost; commonly used; straightforward setup.
Disadvantages	Expensive; complex setup and operation; requires specialized equipment and expertise.	Limited to CCS with headspace; may require costly equipment; not suitable for all formulations.	Lower sensitivity compared to helium leak.	Labor-intensive; qualitative; operator-dependent; requires large sample sizes; destructive; testing takes weeks because of long incubation time	Qualitative; operator-dependent; destructive; less sensitive and prone to subjective interpretation.
Best suited for	CCS qualification, initial development, and critical quality assessments requiring high sensitivity.	Products with headspace requiring gas ingress or stability monitoring (e.g., vacuum-filled CCS).	Routine quality control and batch testing; suitable for many CCS types.	Comprehensive sterility validation, especially in early product development and high-risk assessments.	Cost-effective batch screening and simple integrity checks; situations where lower sensitivity is acceptable.

Your Trusted Partner

CCIT is vital for ensuring the sterility and safety of parenteral products. Selecting a method that aligns with the intended use, stage of the product lifecycle, and quality control needs is essential for ensuring effective and compliant integrity testing. While probabilistic methods like dye ingress have long been employed due to simplicity and cost, the shift toward deterministic methods reflects the need for higher accuracy, objectivity, and sensitivity. Helium leak detection, vacuum decay, and headspace analysis provide robust and reliable testing options that align with modern regulatory expectations and quality assurance practices.[1,2,3]

At Solvias, we offer a range of methods for CCIT, including both probabilistic and deterministic techniques. Our testing solutions align with regulatory authority recommendations, ensuring precise and reliable integrity testing for compliance and safety.

Among our most in-demand methods is vacuum decay testing—a versatile and deterministic approach suitable for various package formats, including lyophilized products and liquid formulations. This method is widely regarded as the industry gold standard for QC package integrity testing due to its enhanced sensitivity and reliability. Sensitivity levels depend on package design, test fixtures, and critical parameters such as time and pressure, all of which we tailor to fit your specific project and product requirements. With multi-chamber instruments, we further enhance flexibility and efficiency, enabling high-quality, cost-effective testing for multiple products on a single instrument.

For further information and details about these analytical testing services, or to get in touch with an expert, contact us at **info@solvias.com**.

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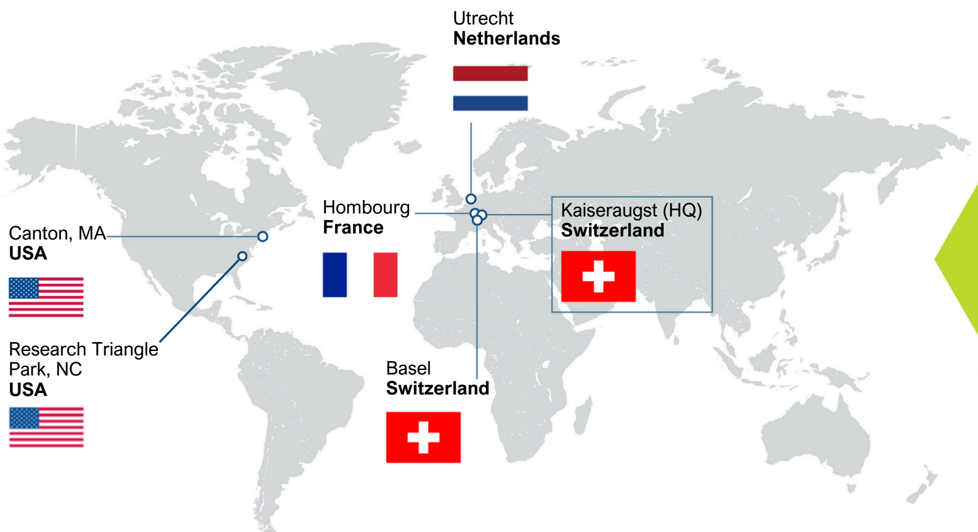

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