Container Closure Integrity Testing of Finished Sterile Injectable Product

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As regulatory guidance has evolved, changes in CCIT testing have also become apparent. In this article, possible CCIT strategy approaches are outlined.

Container closure integrity (CCI) plays an important role in maintaining the sterility and stability of sterile injectable products. The defects that cause a sterile vial to leak are not necessarily detectable by a visual inspection process. Examples of such defects are those that are hidden by the crimp, microscopic cracks and scratches in the glass, or temporary defects such as stopper pop-up that result in temporary container leakage.

New regulatory guidance has triggered changes in industry best practices in the area of CCI testing (CCIT). This article summarizes the current state of container closure integrity testing in the pharmaceutical and biopharmaceutical industries and outlines possible approaches for developing a CCIT strategy.

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Regulatory environment for CCI

Historically, good CCI has been linked to the maintenance of sterility. A container that loses, or does not have, good closure integrity is at risk for microbial contamination. However, the context of CCI has become broader over the years.

An increasing number of formulations have significant sensitivity to oxygen and need to be packaged under an inert atmosphere. Freeze-dried product requires protection against water vapor and is often packaged at a partial vacuum to help with reconstitution and/or seating of the stopper. In these cases, good CCI is necessary not only for the maintenance of sterility but also to maintain critical headspace gas conditions.

Note that, quite generally, a container that is gas-tight will also be tight against microbial ingress. Therefore, the requirement to maintain headspace gas conditions imposes higher standards on CCI than the requirement to maintain sterility.

In light of the importance of CCI for product sterility and stability, regulatory guidance has placed an increasing emphasis on CCI concepts. The current *United States Pharmacopeia* (*USP*) <1207> chapter titled Package Integrity Evaluation—Sterile Products was implemented in late 2016 and represents the most thorough guidance document to date on CCI concepts for sterile injectable product (1).

The chapter gives an overview on CCI testing technologies and approaches for CCI control over the product lifecycle. Traditional CCIT methods, such as microbial challenge tests or blue dye ingress tests, are described as methods associated with probabilistic outcomes having some uncertainty in the results which, in turn, makes such methods difficult to quantitatively validate for the detection of critical leaks (1). The chapter also makes clear that CCIT should be performed throughout the product lifecycle. Deterministic CCIT methods based on non-destructive analytical measurements can be used to generate science-based CCI data that, coupled with a risk-based approach, enable informed decisions about a CCIT strategy in commercial manufacturing.

A draft revision of the European Union's Annex 1 requirements for sterile product manufacturing was released at the end of 2017 (2). CCIT was a popular discussion topic for the revision, and the draft text contains new requirements for CCIT in manufacturing. Other world regulatory bodies, Russia and South Korea for example, have also been putting increasing emphasis on CCI control for finished sterile products. It is clear from these developments that regulators are wanting to see improved industry practices in the area of CCIT.

CCI test methods

USP <1207> provides an overview of CCIT technologies and categorizes them

Table I. Overview of container closure integrity testing (CCIT) technologies.

Deterministic	Probabilistic
Electrical conductivity and capacitance *(high-voltage leak detection)*	Bubble emission
Laser-based gas headspace analysis	Microbial challenge, immersion exposure
Mass extraction	Tracer gas detection, sniffer mode
Pressure decay	Tracer liquid *(blue dye ingress)*
Tracer gas detection, vacuum mode	
Vacuum decay	

Source: Adapted from USP 40 <1207.2>

as being deterministic or probabilistic (see **Table I**). The chapter emphasizes that this overview of CCIT technologies is not exhaustive but is a summary of technologies that have been implemented for CCIT in the pharmaceutical industry and that are described by a body of peer-reviewed literature.

It is important to distinguish between CCI technologies and CCI test methods. Once a leak testing technology has been chosen as the basis for a test method, the chapter emphasizes the need to perform method development studies generating data that demonstrate detection of a critical leak for a specific product container configuration using defined test method parameters (1): "After a methodology has been selected for use, the test equipment operation and performance is qualified. Test method parameters are optimized during method development and confirmed during validation. Thus, a final leak test method is specific to a particular container-closure or product-package system."

Another point emphasized in the chapter is that "no one test is appropriate for all packages or for all leak testing applications." The chapter and its three subsections describe a framework in which appropriate CCI test methodologies are chosen, optimized per product configuration, and a robust validation of the method for detecting a critical leak is performed. In selecting a methodology, "deterministic leak test methods are preferred over probabilistic methods when other key method selection criteria permit."

Package integrity data are generated over the product lifecycle and serves as input for an ongoing database of CCI data (the package integrity profile), which then serves as a risk management tool to ensure that CCI of finished product meets the product quality requirements. The framework described in the chapter is currently driving changes in industry best practices for CCI testing, including:

- Implementation of a 'toolbox' of CCI test methods optimized and chosen on a per product configuration basis rather than the application of a single legacy test method in a one-size-fits-all approach
- Generation of science-based CCI data in robust method validation studies, which demonstrate the detection of a critical leak represented by various types of positive controls.

Statistical sampling and generating science-based CCI data

A big topic of current discussion is how much CCIT is required, especially for commercial batches of finished sterile product. Despite the general consensus that CCI is a critical quality parameter for finished sterile product, the industry has historically expended much more effort on testing for particle contamination than for CCI.

Visual inspection to detect particulate contamination has been a requirement for many years with 100% inspection of finished parenteral product being done manually or by automated inspection platforms. In the context of risk to the patient, a loss of CCI would, in general, be assessed as being just as critical as particle contamination.

The current EU Annex 1 guidelines require 100% leak testing for certain types of product containers. "Containers closed by fusion, e.g., glass or plastic ampoules, should be subject to 100% integrity testing" (3). This requirement is a result of the fact that the inherent failure rate of the sealing process for these types of containers cannot be sufficiently controlled.

The ongoing draft revision of the EU Annex 1 guidelines again states the requirement of 100% integrity testing for fused containers and adds the following requirements for all other types of containers. "Samples of other containers should be checked for integrity utilizing validated methods and in accordance with QRM, the frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A statistically valid sampling plan should be utilized. It should be noted that visual inspection alone is not considered as an acceptable integrity test method" (2). If finalized in this form, these CCIT requirements will require the evolution of best practices for CCIT in the manufacturing environment.

Currently, a small percentage of the industry performs statistical CCIT of finished commercial product. Most companies point to the 100% visual inspection process to justify meeting current CCIT guidance, such as the following from the FDA (4). "A container closure system that permits penetration of microorganisms is unsuitable for a sterile product. Any damaged or defective units should be detected, and removed, during inspection of the final sealed product." The language of the draft EU Annex 1 revision makes clear that visual inspection is not considered an acceptable integrity test method; in other words, the CCI test methods that enable the testing of larger amounts of samples will need to be implemented.

To demonstrate statistical confidence in the process requires the generation of statistical CCI data. However, an argument could be made that a better place to do this in the product lifecycle is in process development and scale-up rather than in manufacturing. The guidance provided in *USP* <1207> to collect package integrity data throughout the product lifecycle so that a package integrity profile database is built up implies an approach in which a significant amount of CCI data are gener-

Figure 1: Schematic of possible approach to generating container closure integrity (CCI) data.

ated outside of the manufacturing environment. The generation of robust CCI data providing knowledge of the container and closure system (which then gives guidance to a CCIT strategy in manufacturing) is also implied in the text of the draft revised EU Annex 1, "the frequency of testing should be based on the knowledge and experience of the container and closure systems being used." **Figure 1** outlines a possible approach to generating CCI data that enables the design of an appropriate CCI testing program in manufacturing.

After validation of the fundamental closure system, data need to be generated to understand if the process introduces risk to CCI. To gain statistical confidence in the process, it would be necessary to perform testing on statistical sample sets. This in turn will require the use of non-destructive deterministic test methods because the probabilistic legacy test methods (blue dye and microbial ingress testing) have limited throughput capability. Testing could be done on either a pilot scale or with test and engineering batches from the manufacturing environment. Once a baseline failure rate has been established, process controls could be implemented to improve the process, if necessary.

Product from the improved process would be tested to quantify the residual risk to CCI after which a decision could be made for an appropriate testing strategy in manufacturing. Packages and processes having a high inherent failure rate that is difficult to control would require a heavier inspection process and vice versa. In this way, the decision for an inspection process design is driven by science-based statistically relevant data.

Summary

The current environment for CCIT of sterile injectable product is evolving. New regulatory guidance recognizes CCI as a quality parameter that is critical for the maintenance of both the sterility and the stability of finished sterile product. New concepts introduced in the regulatory guidance are changing industry best practices and include the following:

- Generate science-based CCI data throughout the product lifecycle to build up a package integrity profile database that can be used as input for risk management.
- When possible, use deterministic CCI test methods that have been validated to detect a critical leak.
- There is no one-size-fits-all CCI test; a toolbox of CCIT technologies that can be optimized on a per-product package configuration is necessary for a robust CCIT program.

Because industry best practices will be evolving as the impact of new guidance becomes clearer, a certain amount of uncertainty in CCIT best practices is to be expected in the near term. However, a general approach that includes the implementation of validated deterministic CCIT methods and the increased generation of science-based CCI data to enable informed risk assessments will help prepare the industry for the future.

References

1. USP, *USP* 40 <1207> "Sterile Product Packaging—Integrity Evaluation" (US Pharmacopeial Convention, Rockville, MD, 2017).
2. European Commission, *EU GMP Annex 1 Revision: Manufacture of Sterile Medicinal Products (Draft)* (Brussels, December 20, 2017).
3. European Commission, *EudraLex, Volume 4, EU Guidelines to Good Manufacturing Practice-Medicinal Products for Human and Veterinary Use*, Annex 1, Manufacture of Sterile Medicinal Products (Brussels, 2009).
4. FDA, *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (FDA, Rockville, MD, September 2004). **PT**

FIGURE IS COURTESY OF THE AUTHOR