# Container Closure Integrity Testing Strategy for Drug-led Combination Products: A Practical Approach

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## Abstract

Drug-led combination products offer patients the ability to self-administer treatments in the comfort of their own homes rather than at the clinic, driving the rapid growth rate predicted for these products over the next decade. Regulatory authorities require demonstration of container closure integrity (CCI) for marketed drug products. For drug-led combination products such as autoinjectors and pen injectors, determining CCI for the fully assembled device continues to be challenging due to limitations with the CCI technologies commercially available. However, a stepwise approach to establishing CCI throughout the product life cycle can generate the data required to show that the product is safe, effective, and sterile through expiry and use. Incorporating a Quality by Design (QbD) approach and a holistic in-process control strategy for CCI during product development and manufacturing can further mitigate the risk for CCI failures.


## Container Closure Integrity Testing throughout the Drug-led Combination Product Life Cycle

One critical quality attribute requirement for drug-led combination products is container closure integrity (CCI) for not only the prefilled syringe or cartridge, which is the primary sterile barrier of the parenteral product delivery system, but also for the CCI of the fully assembled device post-manufacture and beyond. The autoinjector or pen injector is considered secondary packaging because it is not in primary contact with the parenteral product (2). While CCI testing of the syringe or cartridge alone is relatively straightforward, CCI testing of the fully assembled device poses several challenges. The syringe is enclosed inside of the autoinjector, and the cartridge is enclosed inside of the pen injector, making it challenging to perform CCI testing on the fully assembled device with the same sensitivity that can be achieved by testing the syringe or cartridge alone using commercially available deterministic leak detection equipment. The plastic used to manufacture autoinjector and pen injector devices can outgas, and the devices themselves contain many dead volume spaces that trap air and can lead to poor method sensitivity and false rejects when considering vacuum-based CCI technologies. In addition, biologic drug products pose challenges for testing both the syringe or cartridge alone and with the fully assembled device using vacuum-based methods because large molecules, such as proteins, tend to block small defects or leak paths, preventing the detection of leaks. Laser-based gas headspace analysis requires a clear path for the laser to pass through the headspace bubble of the test article; however, often there is no clear access to the headspace bubble through the device, or there is no headspace bubble at all, as is the case with cartridges in pen injectors. Helium leak detection requires the test article to be charged with helium, and high-voltage leak detection (HVLD) requires liquid to be present at the leak site for detection. Neither is possible with most fully assembled devices. To demonstrate CCI for drug-led combination products, the three phases of the drug product life cycle must be considered, and the appropriate CCI testing can be performed during each phase using a stepwise approach.


## Step 1: Test the Empty Syringe or Cartridge during Package Development for Inherent Package Integrity

USP <1207.1> *Package Integrity Testing in the Product Life Cycle – Test Method Selection and Validation* discusses three distinct phases in the product life cycle: Development and Validation (Package Development and Package Processing and Assembly Validation), Product Manufacturing, and Commercial Product Stability (4). CCI testing of the parenteral product delivery system is performed during each phase; however, different CCI technologies can be used, as appropriate, to achieve the desired outcome. For example, during package development, the most important CCI quality attribute to consider is the inherent package integrity of the syringe or cartridge system because those systems provide not only containment but also the primary sterile barrier for the parenteral product. USP <1207> *Package Integrity Evaluation – Sterile Products* (3) defines inherent package integrity as "the leakage rate (or leak size) of a well-assembled container–closure system using no-defect package components. Inherent package integrity is a measure of the leak tightness of a container–closure system, given anticipated variables of material composition, dimension, processing, assembly; package storage, distribution, and use".

In this phase, the components of the syringe or cartridge system are selected based upon stack up analysis, and inherent package integrity studies are performed to demonstrate that the empty syringe or cartridge system is able to achieve the maximum allowable leakage limit (MALL) for the product. USP <1207> (3) defines the maximum allowable leakage limit as "the greatest leakage rate (or leak size) tolerable for a given product–package that poses no risk to product safety and no or inconsequential impact on product quality. The maximum allowable leakage limit for a sterile pharmaceutical dosage form package will ensure the content's sterility, preserve product contents, and prevent entry by detrimental gases or other substances, thus ensuring that the product meets relevant physicochemical and microbiological specifications through expiry and use. For multiple-dose product–packages, the in-use maximum allowable leakage limit is defined as the degree of protection demanded of the closure to limit microbial ingress and product formulation leakage between and during dosage access". In this phase, highly sensitive CCI technologies such as helium leak detection vacuum mode or laser-based gas headspace analysis are used to show that the syringe or cartridge system is able to achieve MALL because these technologies are able to detect leaks in the 0.1 µm range and smaller, where the probability for sterility breaches is less than 0.10 (3).

## Step 2: Test the Product-Filled Syringe or Cartridge after Fill/Finish during Product Manufacturing

Once inherent package integrity has been established for the syringe or cartridge system during the product development and validation phase, non-destructive CCI technologies such as vacuum decay, high-voltage leak detection, or laser-based gas headspace analysis can be used during the product manufacturing phase. These CCI technologies are used for 100% in-line inspection at the end of the fill/finish process, or for off-line inspection when statistical sampling plans are used. Dye ingress, a destructive test, is also often used as an in-process control check when statistical sampling plans are used. A robust in-process control strategy plays an important role during the manufacturing phase to ensure that CCI is achieved not only for the syringe or cartridge system, but also for the fully assembled device. Taking a holistic approach to manufacturing process control builds confidence in the process and demonstrates the ability of that process to repeatedly produce integral container closure systems (6).

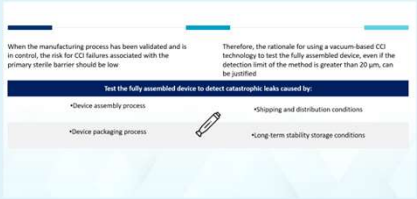

A holistic approach to manufacturing process control includes things like the implementation of established process standards and specifications; an assessment of incoming components for critical quality attributes; testing worst-case combinations of those components for suitability for use; qualification of the fill/finish and manufacturing equipment to establish process capability; using 100% visual inspection to exclude defective components that could affect CCI; using control charts and data trending for root cause analysis; employing in-line vision systems for detection of irregularities in the process; and utilizing statistical sampling strategies for at-line CCI testing (6). When the manufacturing process is consistent and in control, the risk for CCI failures and sterility breaches is reduced for the syringe or cartridge system as well as the fully assembled device. At-line CCI testing using technologies such as vacuum decay, high-voltage leak detection, laser-based gas headspace analysis, or dye ingress confirms that the fill/finish process resulted in integral syringe or cartridge systems that are ready for assembly into the autoinjector or pen injector device. Leaks that range between 1 µm and 20 µm have probabilities ranging from 0.80 - 1 for sterility failures; (8) therefore, it is critical that filled syringe or cartridge systems with defects in this range be detected and rejected before being assembled into the device.

## Step 3: Test the Fully Assembled Device during Manufacturing and Commercial Product Stability

Even when the syringe or cartridge system is integral after the fill/finish process, there is a concern that package integrity breaches can be caused when the syringe or cartridge is assembled into the device; when the drug-led combination product is packaged; during shipping and distribution; and during long-term stability storage. Two approaches can be taken to evaluate CCI at this step: option 1 – remove the syringe or cartridge system from the autoinjector or pen injector device for CCI testing; or option 2 – test the fully assembled device.


For option 1, the same CCI method from step 2 can be used, with additional method development and validation of the process to remove the syringe or cartridge system from the device. The same level of CCI method sensitivity can be achieved; however, steps must be taken to ensure that removal of the syringe or cartridge system from the autoinjector or pen injector device does not cause a breach in the package integrity of the syringe or cartridge system.


For option 2, a second CCI method can be developed and validated to test the fully assembled device. The most viable CCI technologies currently available for this option would be vacuum decay or mass extraction. For vacuum decay, a custom test chamber that is designed to closely fit the dimensions of the autoinjector or pen injector device must be fabricated to achieve the lowest CCI method sensitivity. Due to outgassing from the plastic components of the device, dead volume space inside the device, and the type of product contained in the syringe or cartridge system, this method will likely be less sensitive than the method used in step 2. Here, the purpose of the CCI test is to identify catastrophic gross leaks in the syringe or cartridge system caused by the device assembly process, the device packaging process, shipping and distribution conditions, and long-term stability storage conditions. When the manufacturing process has been validated and is in control, the risk for CCI failures associated with the primary sterile barrier should be low. Therefore, the rationale for using a vacuum-based CCI technology to test the fully assembled device, even if the detection limit of the method is greater than 20 µm, can be justified.




## Conclusion

Drug-led combination products offer patients the ability to self-administer treatments in the comfort of their own homes rather than at the clinic, driving the rapid growth rate predicted for these products over the next decade. Determining CCI for the fully assembled device is challenging due to limitations with the CCI technologies that are commercially available. A three-step approach to establishing CCI throughout the drug-led combination product life cycle can be taken. The first step demonstrates the inherent package integrity of the empty syringe or cartridge system during product development and validation. The second step includes either 100% non-destructive CCI inspection after fill/finish or a statistical sampling plan for off-line CCI inspection and in-process control checks during manufacturing. The third step involves either testing the syringe or cartridge system after being removed from the device or testing the fully assembled device for catastrophic gross leaks in the syringe or cartridge system that may have occurred during manufacturing, packaging, shipping and distribution, and long-term stability storage. This stepwise approach offers a practical CCI testing strategy for drug-led combination products that addresses the critical quality attribute of CCI for the administration of sterile, safe, and effective parenteral products.

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