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ARTICLE

# Key Considerations for Pharmaceutical Packaging: Determining the Limit of Detection in CCIT

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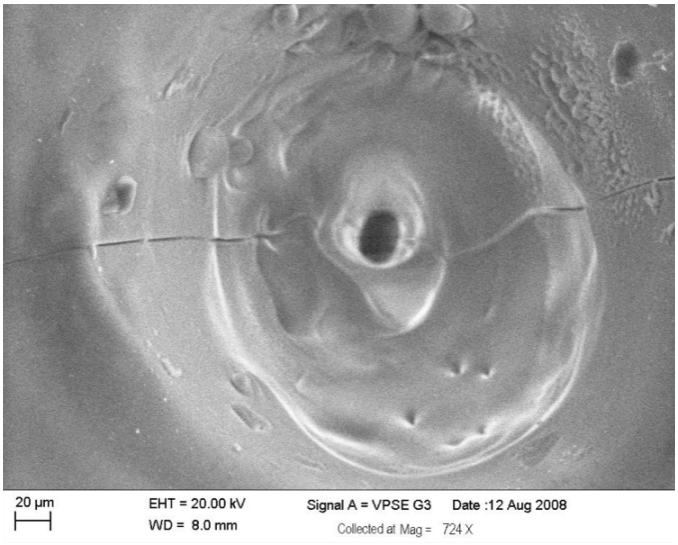
## INTRO

Ensuring the sterility and stability of pharmaceutical products is paramount for patient safety and regulatory compliance. Container Closure Integrity Testing (CCIT) plays a crucial role in verifying that a product's packaging system prevents contamination over its shelf life. Deterministic methods, such as helium leak detection, MicroCurrent high-voltage leak detection (HVLD), and vacuum decay, provide precise, quantifiable, and reproducible results. A key component in validating these methods is the use of laser-drilled positive controls, which to most in the pharmaceutical industry are the "gold standard" to assess the sensitivity and reliability of these testing systems. Validating a container closure integrity test method not only involves establishing a confidence level of detecting varying defects sizes at various locations but also understanding how the housed drug product inside of the container will affect detection results.

## POSITIVE CONTROLS

When validating a container closure integrity test method, positive controls are used to prove detection capability and establish the limit of detection. There are a wide array of approaches to making a simulated defect in container to prove performance. Most approaches fail to provide the right information or introduce an opportunity for false information. Providing an accurate and reliable simulation of a real-world defect is required to show full performance capability. Each method for creating positive controls has nuances in how they perform, with an objective of providing a practical and accurate means of validation.

## POSITIVE CONTROLS




Laser drilled defect 5 µm

Natural Vial Defect

Laser-drilled positive controls are artificial defects introduced into a container-closure package of interest to aid in the evaluation of CCIT method performance, specifically the limit of detection. These precisely manufactured defects provide a controlled and verifiable means of assessing leak detection capabilities. Industry expectation of these laser drilled controls is that they will come with an associated Certificate of Conformance that verifies the defect hole size, typically by measure of flow effective diameter, and/or optical verification. While laser drilling techniques claim that defects can be drilled down to 1µm, it has been seen that any defects drilled under 5µm in size can become problematic due to lower tolerances, clogging from laboratory handling, and product formulation factors. Therefore, the limit of detection of a test method should always take into account the drug product interaction with the container for a holistic approach.

Pipettes and capillaries are two alternatives but are not ideal for many applications. They are a cost-effective approaches to creating controlled orifices, but the defect geometry facilitates easier detection than real-world defects creating a false sense of performance. This is due to pipettes and capillaries being best suited for gas headspace measurements. Complications and intricacies of fluid dynamics introduce an endless combination of factors that can limit or enhance detection such as surface tension, liquid viscosity, surface contact angle, airlocks, and particulate blockage, that make these pipettes and capillaries unsuitable for liquid leak detection.

***All defects are dynamic and risk being impacted. Clogging of defective paths can be looked upon as probabilistic, however, it should be looked upon as problematic. Furthermore, the clogging of defect paths should not be interpreted as a probabilistic event, but rather an inherent risk to any container closure system. Ignoring real-world circumstances, such as the interaction of the housed drug product and potential defect sites, can leave a major gap and introduce risk into the validity of a method when evaluating detection defect size and capability.***

# LIMIT OF DETECTION

The Limit of Detection (LOD) in CCIT refers to the smallest defect size that a given test method can reliably identify. Determining the LOD is the most crucial parameter for establishing the suitability of a CCIT method for detecting critical leaks that may compromise product sterility. Several factors can influence the LOD of a CCIT method. One of these factors includes the sensitivity of the chosen test method. Each deterministic method has a different detection capability, with helium leak detection boasting the most sensitive leak detection down to microbial ingress levels or to the most stringent levels of Maximum Allowable Leakage Limit (MALL) for sterile barriers, for example 6 × 10-6 mbar · L/s (equivalent to 0.1 – 0.3µm). MALL is explicitly referenced in USP <1207> and deemed critical.

Specific to helium and other tracer gas methods, detection of defects at 6 × 10-6 mbar · L/s is typical performance capability. However, creating defects below 3 microns in diameter is highly unreliable. For this reason, helium leak validation is focused on the introduction of a known helium flowrate. As with all tracer gas methods, helium testing is best performed on empty packages, otherwise the liquid contents would block access to the defect for helium to leak out. Given that a helium leak test is typically performed with an empty container and the system performance is challenged with a flowrate that is smaller than can be artificially created, helium leak testing is not typically validated with laser drilled defects. Ultimately, helium is deployed as the most sensitive test method primarily focused on the dry fit and sealing nature of container components.

On the other hand, MicroCurrent HVLD and vacuum decay have reliable detection limits down to around 5µm and are meant to test the container with liquid product. For this reason, these methods do require laser drilled controls for method validation. When successfully validated, a company has the ability to non-destructively evaluate their product package down to a specific defect size with finished product.

# REGULATORY ALIGNMENT

So, this leaves the question, what method does one deploy to validate their container closure system? While proving and defending a method's detection limit can seem daunting, the philosophy of inherent CCI can be applied using multiple CCIT methods. This process would entail testing container closure integrity on the empty container to show that the specified MALL of the closure system can be achieved (i.e. through helium leak detection). Once successfully proven, a less sensitive method that cannot meet the MALL but is far more practical for routine testing can be validated by utilizing laser drilled positive controls with the container's product fill. This thought is further justified by the upcoming update to USP <382>, set to be effective in December 2025. The update specifically emphasizes that sterile products must be able to meet the MALL as also specified in USP <1207>. The update also goes on to detail the need to ensure adequate package integrity and references USP <1207> for guidance on validating a CCI test method.

One final sentiment is that pharmaceutical companies may have the ability to be proactive in their communications with regulatory authorities. In some cases, when requested, these regulatory bodies will give container closure

requirements, among other testing, such as the expectation for a validated deterministic method over a probabilistic method, as well as an expected detection limit criteria. Most probabilistic methods, for example dye ingress, do not have the ability to consistently detect defects below 20µm. It has been seen that many pre-audit requirements are resulting in the expectation that a validated method should have a limit of detection "no less than 20µm", which would show an improvement over a probabilistic approach. Therefore, one should have evidence that they have demonstrated due diligence in selecting the best test method for their product container package, as well as shown the lowest achievable defect size detection through extensive data collection during method development and validation. It perhaps may be more justifiable to a regulatory authority that a method is only sensitive down to 15µm if data has also been collected showing that 5µm and 10µm defects were not able to be reliably detected for their individual package and product combination.

Consulting or partnering with a CCIT industry expert can be advantageous when attempting to navigate through the rapidly evolving regulatory and compliance requirements. Doing so can not only expedite a product's time to market but can ensure the safety of the end user.

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