Container Closure Integrity Testing in Lieu of Sterility Testing in Stability Protocols

INTRODUCTION

When the Food and Drug Administration published "Guidance for Industry: Container and Closure System Integrity *in Lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products" in February 2008, the pharmaceutical industry began implementing container closure integrity testing (CCIT) methods into New Drug Applications (NDA's) and filing "Supplement-Changes being Effected" for ongoing stability programs. In late 2013 both the FDA and CBER reported that many current sterile drug applications now include CCIT in lieu of sterility testing in the stability protocol. Although the blue dye ingress test has long been a standard method in the industry, the recent recommendations from regulators to replace potentially subjective methods has meant that dye ingress is being replaced by more reliable and robust analytical methods for CCIT. One of these methods is laser-based headspace analysis.

METHOD HIGHLIGHTS

The LIGHTHOUSE laser-based headspace method shines light through the headspace to measure gas ingress into a leaking container. For example, a sterile freeze-dried vial sealed under a partial pressure of nitrogen or vacuum

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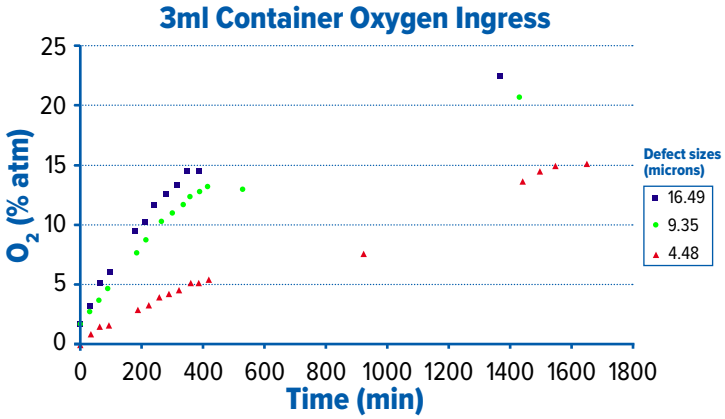
will experience drastic changes in the headspace conditions due to a leak defect. A failure in closure integrity results in the ingress of air and a loss of vacuum – this can be detected with a measurement of the headspace oxygen and/or pressure levels. Based on spectroscopic methods, the headspace measurement is analytical, rapid, and non-destructive. The graph below shows the rise in headspace oxygen levels measured in 3ml containers that were initially sealed under 1 atmosphere of nitrogen. Defect sizes of approximately 5, 10, and 15 microns were laser-drilled into the containers to validate the rise in headspace oxygen levels as a function of defect size. Containers having an initial underpressure in the headspace would experience an even faster rise of headspace oxygen levels.



The rise in headspace oxygen levels in purged containers measured with the non-destructive laser-based headspace method from LIGHTHOUSE.

BENEFITS

- Laser-based headspace is analytical, rapid, and non-destructive.
- Samples are not affected by the measurement and can be monitored over time or re-tested in other ways to gain optimal insight into closure and leak dynamics.
- Both permanent and temporary leaks are detected.
- Laser-based headspace is a very sensitive measurement of the maintenance of closure integrity (and therefore sterility) over the product shelf life.
- Using CCIT avoids the potential issue of false positives for the sterility test in the stability protocol.
- Through the use of certified NIST traceable headspace gas standards, validation of laser-based headspace is relatively straightforward.