Manufacturing Application Note


Introduction

During recent years, the regulatory requirements for container closure integrity testing of pharmaceutical packaging have increased. The FDA states that for sterile drug product, sterility testing alone is not considered sufficient to demonstrate the integrity of the pharmaceutical container/closure. An appropriate integrity test should be used which may include a physical test. In addition, regulators have suggested that 100% integrity testing should be carried out to guarantee the quality and safety of finished product. From the guidance document released by the FDA in September, 2004 titled Sterile Drug Products Produced by Aseptic Processing: Current Good Manufacturing: “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. Safeguards should be implemented to strictly preclude shipment of product that may lack container closure integrity and lead to nonsterility.” For products sealed under full or partial vacuum, the EC Guide to Good Manufacturing Practice, Annex 1, Section 89 states: “Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.”

The nondestructive monitoring of headspace pressure offers a tool for performing container closure integrity inspection for drug packaged under full or partial vacuum. The Lighthouse VISTA/P™ In-Line Vacuum Detection System analyzes headspace pressure in sealed parenteral containers in a rapid and nondestructive fashion. A system with a single optical head can perform
in-line 100% inspection of products at production speeds for the detection and rejection of containers that have leaked above a user-defined reject limit.

Figure 1.
Top view of the VISTA/P™ In-Line Vacuum Detection System.

Experiment
The VISTA/P optical detection technology is based on an innovative optical technique called Frequency Modulation Spectroscopy. Light from a near infrared diode laser is directed through the headspace region of a parenteral container. The laser light is tuned in frequency to match the internal absorption frequency of moisture molecules at 1400 nm. Lighthouse was awarded a patent for this technique in 2003.

The application to monitoring total headspace pressure is made possible by an effect called pressure broadening. It is well known in spectroscopy that the absorption profile of a molecule in the gas phase is a function of the total gas pressure. For lyophilized product, there is always some residual water vapor in the headspace. By scanning the wavelength of the diode laser through a resonance of the water molecule, the pressure broadening of the laser absorption profile can be measured. This technique allows for a direct measurement of the headspace pressure which is accurate and linear over a wide range of pressures (See Figs. 2a & b).
To demonstrate an in-line leak detection application, pharmaceutical product samples were analyzed at a speed of 125 vials/minute for headspace pressure. The forty-six (46) samples were lyophilized product packaged in 10 ml clear glass vials with a specified nitrogen stoppering pressure of 325 torr (430 mbar). A leaking vial was defined to be a vial with a headspace pressure higher than 425 torr (565 mbar). Any vial with a detected headspace pressure greater than the reject limit of 425 torr was to be automatically rejected by the system.

Figures 2a & b.

a) FMS absorption profiles obtained when performing headspace pressure analysis on sealed parenteral containers stoppered at various nitrogen pressures. Note how the width of the absorption profile varies with the headspace pressure. b) In-line measurements of various pressure calibration standards showing the accuracy and linear response of the VISTA/P In-Line Vacuum Detection System over a wide range of headspace pressures.

Results

The results of the experiment are shown in Figure 3. All of the analyzed product samples except for one were found to have a headspace pressure near the specified stoppering pressure. Sample number 45 was found to have an elevated headspace pressure of 520 torr (690 mbar). As this headspace pressure is above the reject limit of 425 torr, this sample was identified as a leaking vial and was automatically rejected by the VISTA/P In-Line Vacuum Detection System.
Results demonstrating an in-line vacuum leak detection application. One vial was found to have a headspace pressure greater than the reject limit resulting in automatic diversion of the vial to a reject bin.

Conclusions
The optical-based sensor platform of the Lighthouse VISTA/P System provides a rapid and reliable method for quantitatively performing automated in-line vacuum leak detection in sealed parenteral containers. A reject headspace pressure level that is above the specified stoppering pressure of the freeze-dried product is defined. Any vial with a measured headspace pressure above the user-defined reject pressure level is assumed to be leaking. These vials are then automatically rejected out of the production line. Validated systems are currently installed and being used in the production environment to perform automated in-line 100% vacuum leak detection of lyophilized product packaged under partial or full vacuum.