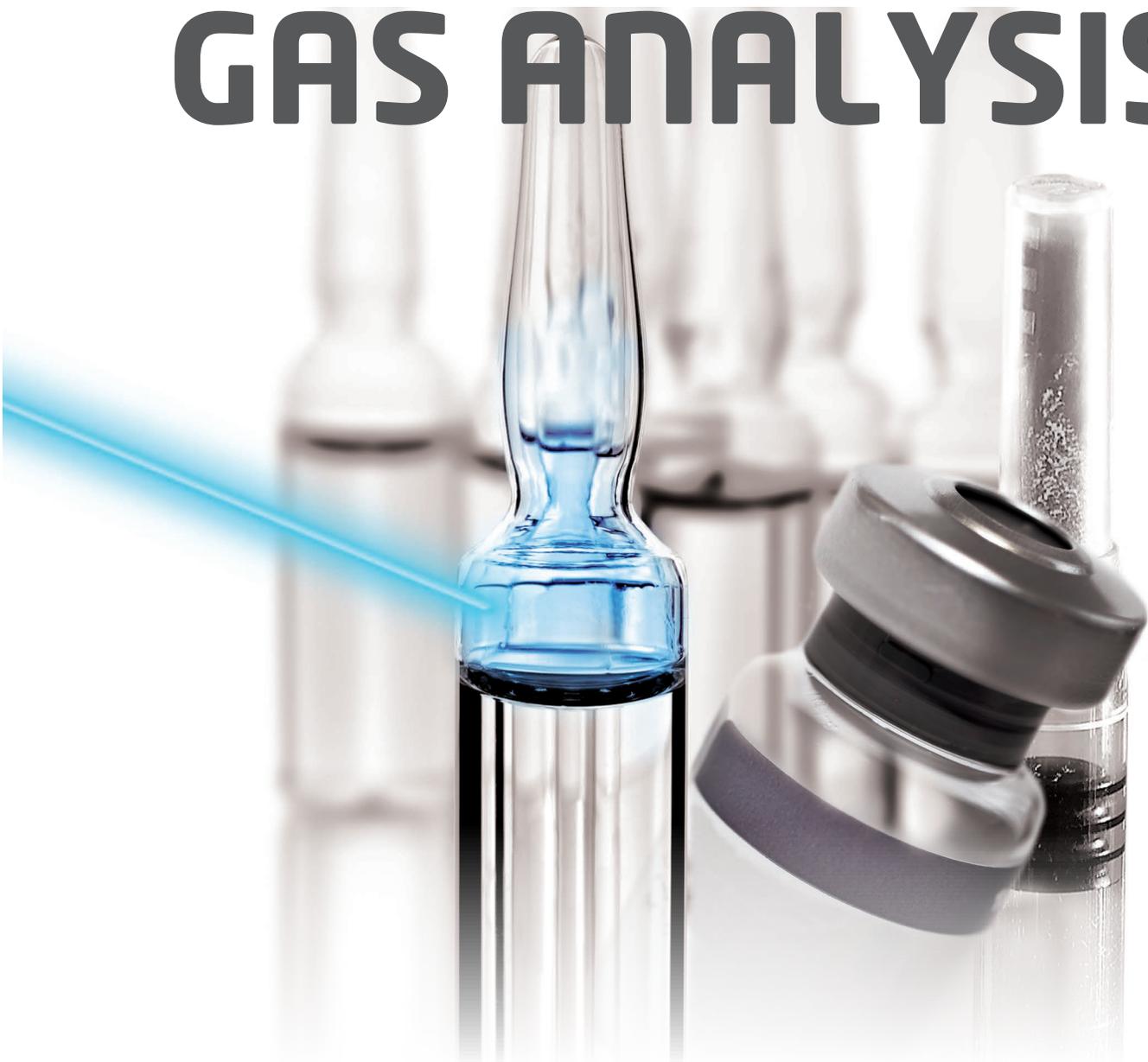




Bonfiglioli
Engineering
Quality Control Solutions



HEADSPACE GAS ANALYSIS



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HEADSPACE GAS ANALYSIS

Headspace Gas Analysis is a laser based, non-destructive and fully automatic inspection of sealed packages, measuring oxygen concentration, residual moisture content and absolute pressure, aiming to verify the maintenance of the headspace conditions created during manufacturing and confirm stability and sterility in filled and finished parenteral packages.

Monitoring the maintenance of container headspace conditions is needed for sterile drugs such as oxygen sensitive liquid products and lyophilized or powdered products; any modification in the headspace pressure, moisture or oxygen level may result in the degradation of the active drug, as well as in the reduction of drug potency and product shelf life.

Traditional headspace analysis methods include test by means of a probe, generally performed on samples at regular intervals during the production cycle: destructive, time consuming and unrepeatable, which prompts the issue of disposing of destroyed products and leaves with no timely feedback on the filling process. Each time out of specification conditions are detected on a sample container, the entire batch is to be rejected, making it most difficult to assess if it's random package closure integrity failure or systematic process unwanted deviation.

Specific requirements for sterile drugs packaged under full or partial vacuum are covered by EU GMP Annex 1. Manufacture of Sterile Medicinal Products, section 123: "Containers sealed under vacuum should be

TECHNOLOGY OVERVIEW

tested for maintenance of that vacuum after an appropriate, pre-determined period". In addition to that, new regulations are expected to enter into force and to include measures to demonstrate the maintenance of sterility over time for drug products into controlled headspace gas packaging.

Therefore the need for an automated reliable, quick and repeatable analysis of the headspace critical gas content, able to monitor all packages in a reference batch.

Bonfiglioli Engineering has been developing innovative solutions in the field of Headspace Gas Analysis with significant advantages over other existing systems.

A Tunable Diode Laser Absorption Spectroscopy (TDLAS) based oxygen or moisture sensor is the core of the inspection system installed in our automation,

a spectroscopic method allowing the detection and quantification of gaseous components concentration.

The principle underlying the TDLAS measurement is based on the Beer-Lambert Law, stating that light transmitted through a given sample at a particular wavelength is a function of the concentration of the substance that is absorbing the incident light. A diode laser beam, at a wavelength optimized for the measurement of a particular gas species, is transmitted through the headspace region of the container and received by a detector after passing through the container itself. Oxygen level monitoring is obtained with light at a wavelength of 760 nm, while wavelength of 1400 nm is employed to obtain measurements of residual moisture level and absolute pressure.



The laser system performance is relatively insensitive to environmental factors such as oxygen presence; therefore, when performing oxygen level analysis, there is no need for purging the surroundings of the container under inspection with nitrogen.

Bonfiglioli Engineering's systems inspection time is shorter than that of other current commercially available ones: this results in a higher level of accuracy at a given production speed or in the same accuracy at a higher output rate. Inspection of non-transparent containers is possible and the system does not require recalibration during operation, meaning standard containers, with known headspace gas level, are not necessary.

Rotary Headspace Gas Analyzer

OVERVIEW

- LVA 600 is an in-line fully automated test unit for performing Headspace Gas Analysis (HGA) of sterile pharmaceutical containers
- LVA 600 is a non-contact, non-destructive unit that employs non-invasive laser-based technology for monitoring the headspace concentration of gases such as oxygen and moisture content
- HGA inspection process is based on the Tunable Diode Laser Absorption Spectroscopy (TDLAS) method which accurately detects and quantifies gaseous concentration levels
- A diode laser beam is transmitted through the container headspace and received by a detector. The target molecule within the container when crossed by the laser beam absorbs the energy depending on the amount of pressure surrounding it. The LVA 600 sensors then measure the laser beam absorption, which will indicate target gas concentration
- The beam wavelength is optimized for the measurement of a



particular gas species:

- > 760 nm for oxygen measurement
- > 1400 nm for residual moisture level and absolute pressure measurement
- HGA is therefore ideal for the accurate investigation of:
 1. glass containers optically transparent to a Near Infrared (NIR) laser beam
 2. the establishment of the proper headspace conditions for products packaged under modified atmosphere
 3. closure integrity in pharmaceutical finished containers
- Multiple laser heads can be installed to increase the speed
- LVA 600 is designed and manufactured for installation in clean areas for less critical phases of sterile product fabrication (Class C and D)



Lab-scale Headspace Gas Analyzer



OVERVIEW

- LF-LASER is a benchtop instrument for performing Headspace Gas Analysis (HGA) of sterile pharmaceutical containers
- LF-LASER is a non-destructive unit that employs non-invasive laser-based technology for monitoring the headspace concentration of gases such as oxygen and moisture content
- HGA inspection process is based on the Tunable Diode Laser Absorption Spectroscopy (TDLAS) method which accurately detects and quantifies gaseous concentration levels
- A diode laser beam is transmitted through the container headspace and received by a detector. The target molecule within the container, when crossed by the laser beam, absorbs the energy depending on the amount of pressure surrounding it. The LF-LASER sensors then measure the laser beam absorption, which will indicate target gas concentration
- The beam wavelength is optimized for the measurement of a particular gas species:
 - > 760 nm for oxygen measurement

> 1400 nm for residual moisture level and absolute pressure measurement

- HGA is therefore ideal for the accurate investigation of:
 1. glass containers optically transparent to a Near Infrared (NIR) laser beam
 2. the establishment of the proper headspace conditions for products packaged under modified atmosphere
 3. closure integrity in pharmaceutical finished containers
- LF-LASER is designed and manufactured for installation in clean areas for less critical phases of sterile product fabrication (Class C and D)





Lab-scale Headspace Generator

OVERVIEW

- LF-HG is a benchtop instrument for manufacturing standard sample containers with known:
 - > headspace oxygen concentration
 - > vacuum level
- Standard sample containers are used for:
 - > Headspace Gas Analysis equipment set-up, verification, qualification
 - > Process validation
 - > Vacuum retention studies for specific container and closure system combinations
- LF-HG handles vials and syringes of various sizes, with automated filling and stopper insertion to the required headspace gas level
- The machine provides multiple service connections for compressed air, nitrogen, oxygen, certified gas mixture and vacuum
- The usefulness and flexibility of this equipment is demonstrated

ed by relevant examples and applications:

- > Headspace oxygen concentration of about 0% to about 20.8% in a modified gaseous atmosphere, replacing air with nitrogen
- > Absolute headspace pressure of about 0 mbar to about 1000 mbar
- > All intermediate concentrations and absolute pressures can be obtained



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