Title:

Bonfiglioli Engineering Headspace Gas Analysis systems for parenteral manufacturing processes: one step beyond product quality and patient safety.

Introduction:

Should sterile drug product manufacturers implement non-destructive Container Closure Integrity (CCI) and Headspace Gas Analysis (HGA) into fill and finish operations? CCI and headspace content verification are two solutions to ensure parenteral product stability and sterility maintenance. Integrity defects as well as failures in the aseptic manufacturing process, including unexpected variability in the nitrogen flushing or vacuum application, pose a risk to product quality and patient safety. Fully automated equipment for evaluating CCI and for measuring headspace gas content is now available. This article presents the innovative solutions that Bonfiglioli Engineering has been developing in the field of HGA and their significant advantages over other existing systems.

Background:

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, likewise in the reduction of drug potency and product shelf life. 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 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 are to include measures to demonstrate the maintenance of sterility over time for drug products into controlled headspace gas packaging. In particular the proposed revision of USP <1207> "Sterile Product – Package Integrity Evaluation" is expected to provide clearer guidance for headspace critical content verification through the entire product life cycle, from stability studies to commercial production stage.

Even with a well-defined manufacturing process in place, it is still almost impossible to keep up with regulatory and quality requirements without a system ensuring a reliable and repeatable monitoring of the headspace critical gas content. Most of the headspace gas measurement methods available on the market are destructive, therefore they are generally performed on samples, at regular intervals, during the production cycle. The main disadvantage of these destructive approaches arises when out of specification conditions are detected and the entire batch is to be rejected.

Headspace Gas Analysis:

Laser-based HGA is a non-destructive and non-invasive technique for measuring the level of gases such as oxygen, moisture content and absolute pressure in the headspace of sterile pharmaceutical containers. HGA is therefore mainly focused on the investigation of the closure integrity of pharmaceutical finished containers and of the maintenance of the proper headspace conditions for products packaged under modified atmosphere or under vacuum. The HGA system presented here uses a technique known as Tunable Diode Laser Absorption Spectroscopy (TDLAS), which is a spectroscopic method allowing the detection and quantification of gaseous component levels in the sub-parts-per-billion (ppb) concentration range. 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 1854 nm is employed to obtain measurements of residual moisture level and absolute pressure. In this HGA system the absorbance of target gas is measured using Wavelength Modulation Spectroscopy which provides a heightened sensitivity and an improved noise rejection characteristic over direct absorption. In addition to that there is no need for extremely fast detection electronics, as required by Frequency Modulation Spectroscopy (FMS), which is another HGA option available in the market.

Bonfiglioli Engineering HGA systems are suitable for inspecting a wide range of different sized glass containers such as vials, ampoules, bottles and pre-filled syringes. In addition to processing the traditional molded and tubular glass containers in both clear and amber color, Bonfiglioli Engineering's latest technology improvements are yielding impressive results in plastic containers as well.

Bonfiglioli Engineering system solutions range from HGA stand-alone units for batch processing and laboratory inspection (model LF-LASER in Figure 1), to In-line equipment, offering 100% inspection capability and allowing a production speed of up to 600 containers per minute (model LVA 600 in Figure 2) with multiple laser units installed.

Figure 1: Lab-scale Equipment LF-LASER

Figure 2: 100% In-line Equipment LVA 600

HGA can also be combined with traditional CCI systems based on Vacuum / Pressure Decay methods as well as with Automated Visual Inspection systems (Figure 3). Similarly, Headspace Oxygen Analysis can be combined with Headspace Moisture Analysis in a single inspection system, offering maximum flexibility when handling products that are both oxygen and moisture sensitive (Figure 4).

Figure 3: Combined Technologies

Figure 4: Combined HGA

This combination of technologies brings unmatched advantages compared to processes that are performed separately: the management system is streamlined, test and inspection data are recorded and documented together, traceability is ensured, floorspace, supervision and maintenance are kept at a minimum

All of the HGA systems presented here provide unique advantages over competitors' solutions including:

- 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;
- Standard containers, with known headspace gas level are not required to calibrate the laser system during operation;
- Inspection time is shorter than that of other current commercially available system: 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.

Furthermore a very brief warm-up time is just another of the pluses making this the perfect fit for any productive environment.

These examples, and other evidence that is available upon request, clearly indicate better performance, accuracy, resolution and robustness of Bonfiglioli Engineering HGA systems.

Conclusions:

In the last years, regulatory requirements for sterile drugs have become more focused on CCI and additionally, many developments in the drug products and container systems have been introduced to the market. The appropriate level of CCI verification as well as the HGA is being recommended now more than ever in the various phases of the product package life cycle.

The use of non-destructive HGA methods overcomes all the limitations of destructive inspection, allowing a targeted, objective and holistic investigation of the entire production. In particular, automated HGA represents a valuable option to ensure parenteral product stability and sterility maintenance in each and every phase of the product life cycle such as development and validation, routine manufacturing and marketed product scenario.

Moreover, the adoption of HGA methods guarantees the reduction of costs connected to reuse of inspected samples that cannot otherwise marketed, thus helping on one hand to guarantee quality and safety of sterile drugs and on the other hand to increase productivity, quality and improve company image.