Title:

XEPICS' 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 (HSA) 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 negative pressure application, pose a risk to product quality and patient safety. Laboratory scale and fully automated equipment for evaluating CCI and for monitoring the level of headspace gas content are now available. This article presents the innovative solutions developed by XEPICS SA that have been developed in the field of HSA 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 packaged under negative pressure; any modification in the headspace pressure, moisture, oxygen and/or carbon dioxide 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": *"Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period"*. In addition to that, new regulations have recently entered into force and including measures to demonstrate the maintenance of sterility over time for drug products into controlled headspace gas packaging. USP <1207> "Sterile Product – Package Integrity Evaluation" is providing a much more detailed 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 HSA 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. HSA 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 HSA 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 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 distinct 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. Lastly, measurements of headspace carbon dioxide concentration require a wavelength of 2000 nm. In this HSA system the absorbance of target gas is measured using Frequency Modulation Spectroscopy which is a robust market standard and therefore it provides a heightened sensitivity and an improved noise rejection characteristic over direct absorption.

XEPICS HSA systems are designed for inspecting a wide range of different sized glass containers such as vials, ampoules, bottles, cartridges and pre-filled syringes.

In addition to processing the traditional molded and tubular glass containers in both clear and amber color, XEPICS' latest technology improvements are yielding impressive results in plastic containers as well.

XEPICS system solutions range from HSA stand-alone units for batch processing and laboratory inspection (model HAS LAB in Figure 1), to equipment offering 100% inspection capability (model HSA 120 in Figure 2).

Beyond that XEPICS can provide a combination system with other container closure integrity systems such as High Voltage Leakage Detection HVLD and automated visual inspection.

Figure 1

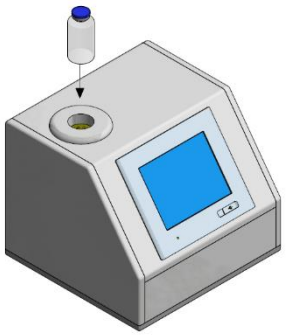
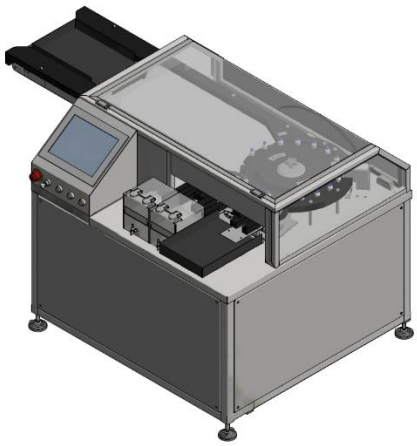


Figure 2



Headspace Oxygen Analysis can be combined with Headspace Moisture (or Carbon Dioxide) Analysis in a single inspection system, offering maximum flexibility when handling products that are both oxygen and moisture sensitive.

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 HSA systems presented here provide unique advantages over competitors' solutions including:

- **Robust best-in-class XEPICS proprietary technology**
- **Non-destructive and non-invasive inspection of liquid, lyo and powder filled packages**
- **Real time inspection data**
- **Reject statistics & inspection result trends**
- **Applicable to vials, ampoules, cartridges syringes, bottles of different headspace composition**
- **Suitable for different glass colors (amber / clear) and types (tubular / molded).**

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 XEPICS HSA systems.

The systems presented here will be unveiled at XEPICS' booth #110C39 during next CPHI Worldwide tradeshow, November 5-7, 2019, Frankfurt (D).

If you want to participate in technical discussions with our experts kindly let us know.

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 HSA is being recommended now more than ever in the various phases of the product package life cycle.

The use of non-destructive HSA methods overcomes all the limitations of destructive inspection, allowing a targeted, objective and holistic investigation of the entire production. In particular, automated HSA 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 HSA 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.