Monitoring and controlling of vaporized hydrogen peroxide bio-decontamination cycles

Sanna Lehtinen

Abstract

This article starts by describing the advantages of using vaporized hydrogen peroxide for bio-decontamination where highly resistant pathogens including bacterial spores might be present. The advantages are its efficacy at room temperature, material compatibility, lack of toxic residue and the relative ease of validation. Several commercially available measurement technologies are described and compared and inline measurement sensors are compared with chemical indicators (CIs, biological indicators (BIs) and enzyme indicators (EIs). The article reports on the results of asking attendees at a Vaisala webinar: "How do you use H_2O_2 ppm measurement today?" and "What are the most important sensor features. Following on from this, the article examines the benefits of using sensors for monitoring and controlling bio-decontamination processes.

Vaporized H_2O_2 applications

Vaporized hydrogen peroxide (H_2O_2) is widely used in room and enclosure bio-decontamination. Typical applications include isolators, transfer hatches (air locks), and cleanrooms. These enclosures are common in life science industries, such as research and the production of medicines, vaccines and cell-based products. Another common use of vaporized hydrogen peroxide for bio-decontamination is hospitals, especially procedures or operating rooms, and patient rooms occupied by patients with communicable diseases. Vaporized hydrogen peroxide is also used in military applications, food and beverage manufacturing, transportation, and construction.

Why vaporized hydrogen peroxide?

Among other benefits, vaporized hydrogen peroxide is easy to use. It destroys numerous micro-organisms, including resistant pathogens such as viruses and bacterial spores. Bacterial spores are highly resistant, dormant structures (i.e. no metabolic activity) formed in response to difficult environmental conditions. The spores remain dormant until favorable environmental conditions occur, at which point they become metabolically active. Vaporized H_2O_2 has been found to be effective against these "sleeping bugs".

Another advantage of hydrogen peroxide is its efficacy at room temperature. Typical bio-decontamination cycle conditions are between 18 to 40°C. Additionally, validating vaporized H_2O_2 bio-decontamination is relatively easy. Further, H_2O_2 is compatible with many different kinds of materials, such as stainless steel. Finally, but increasingly important as industries focus more on operator health and environmental impacts, vaporized hydrogen peroxide leaves no toxic residue, decomposing naturally into water and oxygen. This is a huge advantage, especially in cleanrooms, isolators and transfer hatches used to manufacture medicines for human use. Any residues remaining after bio-decontamination should be washed away with highly purified water, such as WFI (water for injection).

Current measurement technologies

Because the effectiveness of vaporized H_2O_2 is well documented, there are several commercially available measurement technologies for vaporized hydrogen peroxide concentration, each with their own advantages and disadvantages. Table 1 shows a simple comparison of commonly used sensor technologies. Some are used to detect very small concentrations (ppb) and others measure higher concentrations (ppm). The benefits derived from an initial investment in equipment varies tremendously because equipment ranges from measurement sensors to complex analyzing devices.

It is worth mentioning that equipment based on NIR technologies, as well as gas analyzers, is not fit for

Table 1: Common technologies for measuring vaporized hydrogen peroxide.

Technology	Benefits	Challenges	Measurement parameters
Electrochemical cells	Sensor cell easy to change	Short lifespan, repeatability	ppm (H_2O_2)
NIR (near infrared technologies)	Stable, for R&D	Expensive, big size, not for low measurements	ppm (H_2O_2/H_2O), a (H_2O_2, µg/l), a (H_2O, g/m^3)
Gas analyzers (laser technology)	High selectivity, detection limit, low measurements	Expensive, big size, heavy, non-continuous measurement	ppb, only low level measurements
Capacitive thin-film polymer sensors	Several measurement parameters, stable, repeatable, small size	Not for safety applications (≤1 ppm)	RH%, RS%, °C, ppm (H_2O_2), absolute H_2O_2 and H_2O, H_2O ppm by volume, water vapor saturation pressure (H_2O and H_2O_2+H_2O), dew point temperature, vapor pressure (H_2O and H_2O_2)

monitoring and controlling bio-decontamination due mainly to price, size and/or H_2O_2 vapor concentration measurement range.

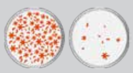
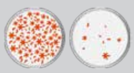
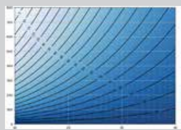
Proving bio-decontamination efficacy

The effectiveness of bio-decontamination cycles is evaluated based on the results of indicators (biological, chemical or enzyme indicators). Biological indicators (BIs), which may take various forms, contain *Geobacillus Stearothermophilus* spores. These rod-shaped, Gram-positive, spore-forming, and thermophilic (heat loving) bacteria are the accepted, worst-case organisms that must be used in bio-decontamination validation runs. It is accepted that if your process can destroy these organisms, it can basically handle all others. A 6-log reduction of BIs is proof that the cycle was effective.

While this is the industry norm, it is expensive and time-consuming to ensure an adequate number of indicators, then test, locate, collect, incubate and analyze the results. In addition, there are known issues with BIs, foremost are "rogue indicators" that will show spore clumps that will not be deactivated even after long exposure times. Because of the non-uniform quality of commercially available BIs, the industry norm in usage is to add triplicate BIs at worst-case scenario positions in bio-decontamination validation – see Coles.[1]

Companies that rely on bio-decontamination processes often also measure vaporized hydrogen peroxide concentration, indirectly or directly, in their target area. Indirect measurements are performed by evaluating the amount of hydrogen peroxide liquid on the heated plate (ml/minute, g/minute or g/m³ created) during the vaporization processes. Direct measurements provide a value for the actual air ppm concentration of vaporized H_2O_2 in the target area. These direct measurements are obtained with an inline measurement sensor. Table 2 is a comparison of indicators to inline measurement sensors. Inline measurement sensors collect continuous measurement of H_2O_2 ppm concentration data, often with other parameters such as temperature and humidity. However, an inline sensor doesn't indicate log reduction. Biological and enzyme indicators are used to obtain this information, providing the data to calculate the log reduction of micro-organisms during decontamination cycles.

Table 2: Vaporized hydrogen peroxide indicators versus inline measurement sensors. RH = Relative Humidity, RS = Relative Saturation, SAL = Sterility Assurance Level.

	Chemical indicators (CI)	Biological indicators (BI)	Enzymatic indicators (EI)	Measurement sensor; Vaisala HPP272
PROS	Inexpensive Easy to use	Quantitative results	Quantitative results Instantaneous reaction	Continuous, inline measurement gives knowledge of the process throughout, allows for corrective action if process parameters aren't met
CONS	Gives "±" value only Non-quantitative	7-day wait for results, requires qualified lab and personnel	Manual process, no continuous measurement data	No value for log reduction, used in combination with BIs/EIs
Measurement results	Change in color; H_2O_2 concentration +/-	Reduction of micro-organisms (SAL min. 10^{-6}) 	Reduction of micro-organisms (SAL min. 10^{-6}) 	H_2O_2 ppm, Relative Humidity, Relative Saturation and Temperature 

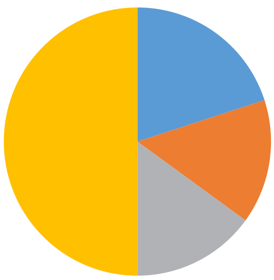


Figure 1: How do people use vaporized hydrogen peroxide ppm measurements today (n=20)?

Listening to Industry

In a webinar presented in June 2019 by Vaisala: "*From Monitoring to Controlling with vaporized H_2O_2 Sensors: Why, How & a Case Study*", attendees were asked: "**How do you use H_2O_2 ppm measurement today**"? Figure 1 shows attendee answers. Half of the respondents do not measure H_2O_2 ppm concentration at all. For those who do measure ppm during bio-decontamination, 20% use it for monitoring, 15% for controlling and 15% for both monitoring and controlling purposes. If these results demonstrate the current state of industries using vaporized hydrogen peroxide for bio-decontamination, this indicates an enormous opportunity for improvement that can become a competitive advantage for firms using vaporized hydrogen peroxide in bio-decontamination. With inline monitoring and control of vaporized hydrogen peroxide in real time, continuous concentrations can provide better process control, improved documentation for change control, validation and compliance, as well as time and cost savings in validation.

Monitoring and controlling of bio-decontamination cycles

When we say monitoring we usually mean that process parameters are followed continuously during a process using an inline measurement device. Inline measurement involves a sensor located inside the real test environment throughout the process. In bio-decontamination, inline measurement can provide values for related process

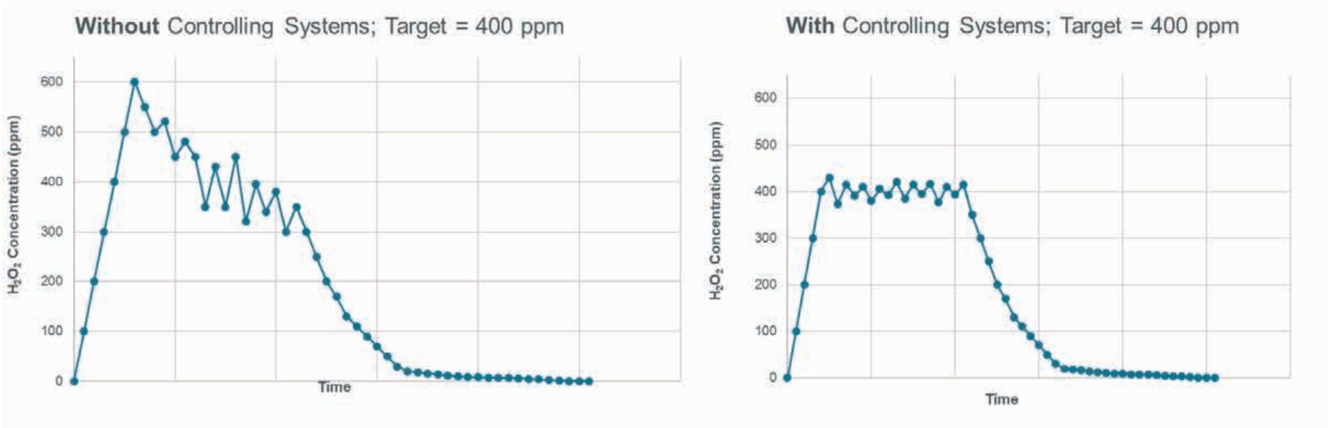


Figure 2: Example of two bio-decontamination processes with and without inline measurement for process control, both with a target level of 400 ppm of vaporized H_2O_2

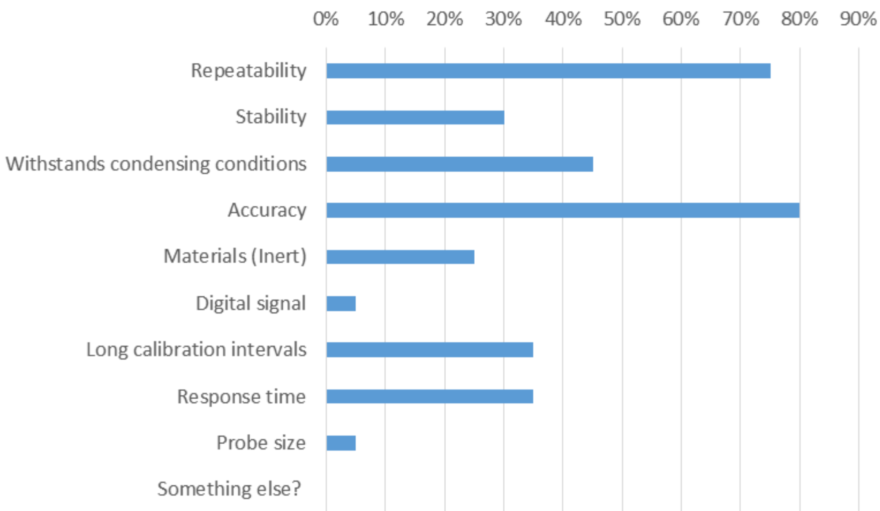


Figure 3: What are the most important features for a measurement sensor used for controlling purposes? (n=20, multiple selections enabled)

parameters such as H_2O_2 vapor concentration (ppm), humidity and temperature.

With inline measurements providing continuous measurement data, operators see real-time data throughout the cycle. An understanding of KPIs (key performance indicators) like temperature, humidity and H_2O_2 ppm values throughout a cycle gives assurance that the process is going according to plan. Often this can decrease the number of biological, chemical or enzyme indicators required in recurring validation runs because the inline measurement data is available. Further, inline monitoring data enables good documentation practices, recording and reporting during batch manufacturing and validation runs.

In addition, monitoring processes also between validation runs enables you to see changes in the environment (°C, %RH) that might have a tremendous effect on process control. This idea was demonstrated by Nieskes.[2] More information about how environmental conditions can affect the achievable ppm concentrations can be found in a Vaisala white paper.[3]

A sensor with good repeatability not only provides monitoring data, but can be used to control the decontamination process. It is increasingly common for companies using inline bio-decontamination measurement sensors to use sensor data to control a vapor generator in a room or isolator. With the sensors integrated to control systems, the H_2O_2 vapor generators can be controlled, not based on predetermined injection profile of H_2O_2 liquid, but based on actual inline measurement values. This method provides flexibility and enables a fast response to any changes in environmental variables during decontamination cycles. Inline measurement used to control processes also automatically decreases the variability of conditions from batch to batch and leads to more stable ppm levels in processes. Validation efforts can be reduced by having reliable data throughout a process.

This method of monitoring and controlling critical process parameters follows the PAT (Process Analytical Technology) ideology. Equipped with real-time data on processes, operators can immediately respond to changes or unexpected events. Figure 2 offers an example of two bio-decontamination processes; one with and one without inline measurement used for control. As shown, processes controlled based on real-time measurements facilitate more stable ppm concentrations for bio-decontamination cycles. When the process is controlled by the actual conditions, rather than pre-determined calculations and assumptions, the system is made more efficient at achieving process requirements.

Industry speaks: What is needed in a sensor?

When attendees in Vaisala's webinar mentioned earlier were asked: "**When measuring for control, the most important sensor features are…**" the answer was a clear preference for accuracy and repeatability, as shown in Figure 3.

Based on this feedback, the three most important features of a sensor used for control are: accuracy, repeatability, and withstanding condensing conditions. Other characteristics like long calibration intervals, response time, stability, and inert sensor materials were selected by responders. Digital signal and probe size might also be important in some circumstances.

* See https://www.vaisala.com/sites/default/files/documents/PEROXCAP-TechNote-B211653EN-A-LOW.pdf

There are a number of companies that manufacture instruments for measuring the concentration of hydrogen peroxide vapor. For obvious reasons, the author is most familiar with those manufactured by Vaisala. The Vaisala HPP270 series probes, with PEROXCAP® sensor using thin-film polymer technology, were designed to fulfill all of the requirements listed.* This technology represents a unique measurement principle and is created based on Vaisala's proven HUMICAP® humidity measurement technology. Three-in-one HPP272 sensors measure hydrogen peroxide concentration (ppm), and temperature and humidity, referring to both relative humidity and relative saturation. This gives exact hydrogen peroxide readings in ppm throughout the whole bio-decontamination cycle. Dew point and vapor pressure measurements are also possible.

"Based on the survey experience of sterilization and bio-decontamination professionals,there is still room for improvement in the use of monitoring and control for bio-decontamination processes."

A Finnish vapor generator manufacturer Cleamix uses Vaisala's HPP272 sensor in controlling H_2O_2 vapor generator cycles. While selecting a sensor for their vapor generators, their control sensor requirements were:

1. Sensors need to be rugged enough to maintain accuracy through multiple processes.
2. Multiple measurement parameters are required to provide better understanding of process conditions (ppm, temperature, %RS, %RH, dew point, vapor pressure).
3. Sensors must provide a digital output signal. Analog signals are subject to deterioration from noise during transmission and write or read cycles. Communication should be achieved via Modbus RTU. HPP272 and a portable vaporizer that can use RS-485 allowing communication in a local area network, nearly resistant to electromagnetic interference.
4. Superior sensor stability, with calibration only once a year.
5. Ability to control condensation. The sensor described measures %RS (relative saturation) that gives the ability to maintain dry conditions with minimum condensation in enclosures or rooms during bio-decontamination processes.

Future trends for monitoring and controlling bio-decontamination processes

Bio-decontamination cycles are still often monitored and controlled by indirect measurements of added H_2O_2 liquid (mass or volume per time or air volume) on the heated plate. However, monitoring and control of bio-decontamination cycles based on inline, real-time measurement increases our knowledge of bio-decontamination processes, allowing users to witness and respond to changes in the environmental conditions. It is well understood that temperature and humidity have a huge effect on validated bio-decontamination cycles. Controlling bio-decontamination cycles based on real-time measurement can decrease batch-to-batch variability and simplify validation. For these reason both OEMs (Original Equipment Manufacturers) and end users are increasingly using inline monitoring with control in their vaporized H_2O_2 bio-decontamination processes for vapor generators, isolators and transfer hatches.

Based on the survey experience of sterilization and bio-decontamination professionals, there is still room for improvement in the use of monitoring and control for bio-decontamination processes. Several measurement devices are available on the market such as Vaisala's HPP272, so lack of technology is not the problem. The PAT ideology is proven and accepted in drug manufacturing. We believe that bio-decontamination, as a critical process, is moving toward adopting PAT mechanisms to ensure quality, control costs and reduce waste.

References

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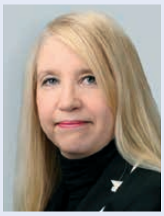

Sanna Lehtinen is a Product Manager at Vaisala. She has worked as an electronics designer and with life science product management in leading international high tech companies for 20 years. At Vaisala, Sanna ensures product quality and road mapping, gathers industry insight, develops leading products for demanding customer needs and produces relevant customer-facing material. Sanna holds an MSc in Biomedical Engineering from Tampere University of Technology and MSc in Economics from Helsinki School of Economics.