



Mastering VHP Sterilization

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In the pharmaceutical industry, maintaining sterility is a must. While there are several sterilization processes available, Vaporized Hydrogen Peroxide (VHP) is a popular and reliable method that provides the highest level of microbial control within a given facility, according to Pharmaceutical Technology. Despite this popularity and reliability, there are critical considerations for the application of VHP technology. Temperature and humidity play major roles in the VHP process, and accurate monitoring of both parameters is essential. Although this monitoring presents the greatest challenge to the application of VHP, the use of proper techniques and best practices ensures successful decontamination and sterilization.

The Basic Science of VHP

The typical VHP cycle consists of three or four phases and uses a liquid hydrogen peroxide (HP) solution, typically 35% to 59%. The process begins with dehumidification. A target range of humidity is between 30% and 50%. The conditioning phase is an optional ramp phase during which the concentration of VHP is slowly increased in the target decontamination zone. Injection rate affects ramp-up and final concentration. A typical concentration for room application in pharmaceutical facilities ranges from 150 to 700 ppm. Target concentrations are sustained throughout the decontamination phase and, once completed, aeration can commence. During the aeration phase, the target zone is purged with fresh air to drive out vaporized HP. In order to ensure success during this process cycle, it is important to monitor and control several variables that can affect efficacy.

Temperature, humidity, VHP saturation, concentration and distribution can all affect the efficacy of the decontamination process. Isolator temperature and humidity directly affect the maximum achievable concentration of HP generated in the gas state. Saturation must be monitored throughout the process, because it is important to stay below the condensation line for HP. Concentration of HP is typically 150-700 ppm for



room application, with the HP injection rate governing ramp-up and final concentration. Room distribution can be affected in several unexpected ways. Although VHP has a strong material compatibility profile, certain materials can absorb and/or contribute to the breakdown of VHP. These materials include galvanized steel, nylon, anodized aluminum, copper, titanium dioxide, latex gloves, and freshly painted or improperly cured painted surfaces. Standing water can also alter distribution by absorbing VHP.

VHP Process Development

Any process development of VHP starts with certain project planning considerations. In all cases, each organization needs to develop a fumigation management plan document. Project planning templates are available and can be used to review the various logistical aspects needed in order to execute a VHP program. As a general guideline, most organizations will need to define the purpose and scope of the decontamination. Team players, including stakeholders and support personnel, need to be identified. A site visit should be performed to review schematics, HVAC and electrical capabilities. Site control and security have to be maintained, and site signage should be addressed. The target zone needs to be precleaned, smoke detector systems need to be off-line, safety buffer zones should be defined, and monitoring plans must be in place.

After project-planning considerations have been addressed, the next step in process development is mapping the isolator, which can be accomplished in several stages. Temperature distribution and equilibrium studies can be obtained by using calibrated thermocouples throughout the isolator to record air and surface temperatures. These parameters directly affect VHP concentration. Gas distribution studies can then be conducted (DEI), which monitor high and low concentrations of HP. These Draeger indicators are also effective for monitoring room and technical spaces for any fugitive emissions.

Biological indicators (BIs) should then be positioned around the thermocouples. This will aid in developing D values for the isolator, which is the time required to reduce spore population by 90%, or one log. A typical BI used for this application is *geobacillus stearothermophilus*, a bacterial endospore that is the most resistant to VHP, typically



three to six log. Triplicate BIs are placed at suspected challenge sites based on the temperature profile, chemical distribution, and a geometric coverage requirement of at least five to 10 BIs per cubic meter. While injecting, BIs are serially removed in five-minute intervals to establish the lethality rate. Cycles are repeated with increasing exposure until total kill is achieved. This lethality study will produce the worst-case scenario needed to start cycle development. A good starting point is to use decontamination cycles that are longer than six times the D value. Isolators are validated using BIs inoculated with greater than 10^6 spores. BI resistance studies should be performed at cycle conditions and validated using a third-party laboratory.

Further improvement in process development can be accomplished by reducing cycle time. Investigative efforts should be directed toward exploring injection rate increases or aeration temperature and airflow. An additional benefit to reducing cycle time is the reduction of residual HP concentration, which will also limit personnel exposure.

Challenges of Monitoring the VHP Process

The physical and chemical nature of VHP produces both process advantages and monitoring challenges. One of the advantages of HP is that at increased concentrations, it is a very aggressive oxidizer, and this basic property allows it to destroy a wide range of pathogens at relatively low concentrations. However, because of this chemical property, VHP also produces unique instrumentation challenges related to condensation and contamination. The two problems commonly encountered with traditional moisture sensors are that long-term reliable humidity measurements are not possible during the VHP process, and eventually conventional humidity sensors are damaged or destroyed by the VHP process.

During the VHP process, the temperature and humidity sensors have to operate under a certain amount of positive pressure and must be resistant to HP condensation and the resultant contamination. The effects of the VHP process on conventional temperature/humidity sensors begin with the degradation of sensor circuits. This degradation affects accurate measurement and recording by increasing sensor response time, which is detrimental to process control. Depending on the sensor design, the accuracy and repeatability continues to degrade as sensor performance



declines. The long-term oxidative effects of HP eventually lead to premature sensor failure. Even accurate and reliable humidity sensors in VHP service are damaged or can fail entirely due to the corrosive nature of VHP. Bagging or isolating the sensor during the sterilization process is a common, low-tech practice geared toward reducing contamination and degradation. However, this practice prevents the instrument from taking multiple readings during the VHP cycle.

Another consideration with various types of instrumentation is operating costs related to consumables, routine cleaning and maintenance, and repeated calibration. Dew point refractory instruments, while being sensitive to VHP monitoring, require repeated routine maintenance in order to remain clean. Calibration is a problem with some designs, and material and operating costs can be higher compared with VHP because of the cost of consumables.

The challenge that condensation and contamination pose with standard design temperature and humidity sensors can be overcome by making the sensor resistant to HP degradation while retaining all of the performance features and the size and cost advantages. For example, Testo, Inc. has developed a unique protective active filter, called a G8 filter, which replaces a standard metallic filter on a traditional transmitter probe. This particular design uses no consumables or threads on the probe directly in place of the previous filter. When an ambient VHP and air mixture pass through this filter, it is converted into the by-products of water and oxygen. The result is the elimination of reactive VHP and the production of a benign, internal microenvironment climate, which consists of water vapor and oxygen. Consequently, a standard temperature and humidity sensor can be used for accurate, fast, long-term moisture measurement. A secondary benefit is the elimination of VHP condensation on the sensor, which further ensures a faster response time and a much longer sensor life in day-to-day practice.

The vaporization of HP is another important parameter to monitor during the VHP process. The amount of vaporized HP affects the condensation line, and it is known that microbial kill increases near the condensation line. The amount of vaporized HP directly affects the dew point of the mixture of humid air and VHP. An accurate dew point measurement is essential in determining the dew point distance, which is the difference between the atmospheric dew point and the mixture dew point. Depending



on the liquid HP concentration ratio, the mixture dew point is usually significantly higher than the standard water vapor dew point. Because the dew point distance is related to temperature, the goal is to keep some distance between ambient process temperature and dew point temperature. An accurate dew point can be calculated by using the concentration of the liquid HP percentage by weight. Process instrumentation is also available to aid in this process.

Pharmaceutical Applications

Presently, the VHP process is widely used. There are over 1,200 systems installed worldwide in pharmaceutical research, biocontainment, and manufacturing facilities with more than 15 years of validated use. Mobile VHP units are available that can be used solo or daisy-chained for larger spaces. With multiple generators, up to 200,000 ft³ can be decontaminated in a 24- to 48- hour period.

Gaseous decontamination has a multitude of applications. This process can be used for contamination remediation and bioburden reduction. Bioburden reduction is a useful measure prior to the occupation of new or renovated facilities, and when a product or population change has occurred. Situations that require equipment transfer or service in areas where biological hazard may be in use are another useful application. Typical pharmaceutical facility applications include aseptic manufacturing rooms, tissue culture rooms, warm rooms, cold rooms, lab animal research (LAR) facilities, LAR equipment, biocontainment facilities, biosafety cabinets, incubators, and other small enclosures.

Safety and Efficacy

There is a wide choice of sterilants on the market, including alcohols, acids, phenols, halogens, chlorine dioxide gas and formaldehyde. Historically, formaldehyde gas has been the agent of choice. It was not until recent years that chlorine dioxide gas and VHP became available. Although each agent has particular safety issues to consider, VHP has several positive attributes.



At very low concentrations, typically 0.5 – 1 mg/l @ 25°C, VHP is sporacidal across a broad spectrum of microbial agents. This attribute makes it effective for use in pharmaceutical applications, and the low-use concentration reduces process time. Some cycles are as little as 28 minutes. Other sterilants, such as ethylene oxide, may take hours.

The typical use concentration of VHP is 150-700 ppm. The typical use concentration of chlorine dioxide gas is 350-1500 ppm, and formaldehyde is 8,000-10,000 ppm. Unlike these other gasses, VHP naturally degrades into benign by-products. It has been shown that in less than two hours, VHP will degrade from 600 ppm to 75 ppm, with no aeration. This attribute is beneficial in limiting personnel exposure.

When considering VHP typical use concentrations, degradation properties, migratory properties, and OSHA exposure limits, VHP offers less exposure risk to personnel and product outside the target decontamination zone when compared with other gaseous agents. VHP provides decontamination at ambient temperatures and low concentrations, has a strong record of efficacy data, and can be easily replicated during live decontamination in terms of efficacy testing. It is a controlled process with real-time concentration monitoring throughout the target zone, has a strong safety profile, nontoxic by-products, and is compliant with EPA registration requirements.

For any facility considering VHP process development, a management plan document needs to be in place to direct that development. Because VHP is containable in a manner not suitable for other sterilant gases, this process can be adapted to many facilities not otherwise designed for VHP. Although monitoring the VHP process offers unique challenges, this difficulty can be easily overcome with specific instrumentation.