The Monitoring of Isolators and Enclosed Spaces which have been subject to Biodecontamination by Hydrogen Peroxide Vapour

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Introduction.

Vaporised Hydrogen Peroxide (VHP) biodecontamination is used to achieve surface sterilisation of the exposed, clean and dry surfaces of components, containers and working areas of isolators and other devices used in pharmaceutical processing. This can include the aseptic processing of sterile medicines and laboratory applications such as sterility testing.
VHP is bactericidal, fungicidal, sporicidal and virucidal and produces hydroxyl radicals, which rapidly cause cell death.
VHP may be supplied by a generator that delivers the vapour phase agent to an isolator body, transfer chamber or other enclosed device. The cycle has various stages, which include maintenance of the required concentration of hydrogen peroxide during the biodecontamination process. In this stage the hydrogen peroxide may be maintained in the form of a vapour or it may be allowed to form a layer of condensate on exposed surfaces to be sterilised.
Appropriately controlled VHP biodecontamination has a number of advantages in aseptic processing of medicines. This includes a reliable, reproducible cycle capable of sterilising surfaces to a known Sterility Assurance Level (SAL). However VHP biodecontamination does rely on the entire Isolator system maintaining its integrity both during the biodecontamination procedure and subsequent processing of medicinal products.
The application of a VHP biodecontamination process to isolators is not considered to be a sterilization process in the same way as, for example, a sealed container subjected to a validated dry heat, moist heat or irradiation process.

The principal aim of this paper is to provide guidance on the requirement for microbial monitoring during aseptic preparation sessions although other aspects are included.

Note: - This document should be used in conjunction with the document ‘Sampling Programme for GMP Grade Controlled Environments Section 10 Units, Active Air Samples Settle Plates, Surface Samples, Locations and Number of Samples’.

Process Considerations.

The VHP process is applied to items enclosed in a sealed chamber, which may be an isolator, sterilisation chamber or transfer chamber. These devices may also be supplied with High Efficiency Particulate Air (HEPA) filtered air to enable maintenance of GMP grades of environment. The VHP may be delivered through these filters, in which case the filter medium will also be sterilised, or directly into the chamber bypassing the filters. If VHP is delivered through the HEPA filters the cycle time is significantly greater because the filters adsorb vapour leading to an increased time to achieve the required concentration and further time required to desorb vapour at the end of the cycle.

An advantage of delivering VHP through the HEPA filters is compliance with the PICS document on Isolators.

Limitations

Processing with hydrogen peroxide is subject to some limitations, which include: -

- Contact between items and surfaces can result in inadequate exposure to vapour resulting in failure to sterilise all components and surfaces.
- Changes in loading pattern can affect vapour distribution and compromise the biodecontamination process.
- HEPA filters fitted to isolators may be damaged and allow unfiltered air to enter the controlled work area resulting in subsequent microbial contamination.
- The effectiveness of VHP biodecontamination on the products, components and process is dependent on the integrity of the whole isolator, particularly with negative pressure isolators.

Commissioning and Validation of the VHP Sterilisation Process

It is important that the VHP biodecontamination cycle is developed individually for each separate circumstance.
Following cycle development there are three principal components for the commissioning and validation of the process.

- Commissioning and validation of the biodecontamination process of the empty Isolator

- Commissioning and validation of the biodecontamination process of the loaded Isolator. There may be several loading patterns, which require validation.

- Monitoring of the aseptic production sessions to ensure that the whole system and process maintains a sterile environment.

Commissioning and Validation of the empty and loaded Isolator

This is required to confirm satisfactory VHP biodecontamination process performance. Monitoring is performed using chemical and biological indicators. The same type and source of chemical and biological indicator, and preferably the same batch, should be used throughout. It is particularly important to ensure that Isolators are free from leaks and tested regularly for absence of leaks. The VHP biodecontamination process is only valid if the integrity of the isolator is secure and continues to be secure.

Chemical Indicators. Indicator strips containing a reagent sensitive to the concentration and exposure time of hydrogen peroxide. The strip usually contains a reference indicator that does not change colour on exposure, and a test indicator that responds to hydrogen peroxide exposure. Comparison of

the two areas may be used to assess the extent of exposure of hydrogen peroxide vapour.

Biological Indicators. Stainless steel disks usually dished on one side and coated on the dished side with a spore suspension of *Geobacillus stearothermophilus* ATCC12980 to provide a known population of spores. The indicator is usually presented in an envelope which has one side made from gas permeable paper (Tyvek). The indicators are supplied with certification confirming the D value and spore population of the indicators. Biological indicators can provide a reliable measure of process lethality.

Satisfactory isolator performance must be verified before commencing VHP processing. This is followed by validation of the biodecontamination process of the empty Isolator and, when this has been completed satisfactorily, the validation of the biodecontamination process of the loaded Isolator chamber. This is performed with typical load patterns using chemical and biological indicators. These are placed throughout the Isolator chamber and locations in the load to establish adequate and uniform penetration of vapour into all areas of the isolator and load. Validation tests are repeated until satisfactory and reproducible performance is established for every load pattern to be used. Typically at least three satisfactory validations are required for each loading pattern. Since there may be numerous permutations of loads during day-to-day operation a limited range of maximum load patterns should be established based on surface area and container types.

Requalification

Requalification of the VHP biodecontamination process should be performed annually or following a lengthy period where the equipment is unused. Typically this would be carried out following the service and calibration of the VHP generator by the supplier and include the maximum load pattern in terms of surface area.

Monitoring of routine VHP Bio decontamination

Following the completion of satisfactory commissioning and validation of the Isolator and VHP biodecontamination process the regular, routine VHP process may be monitored using a reduced number of chemical and biological indicators.

- This should continue to include at least one chemical indicator for each isolator chamber cycle.

Monitoring of Aseptic Production Sessions

Sessional monitoring is required to ensure that the whole system has retained its initial integrity as a Grade A environment for the aseptic production of critical medicinal products. This is carried out using finger dabs, settle plates and contact plates or swabs.

The format and system of working with Isolators will vary with each installation. Therefore the frequency and extent of monitoring will be decided locally. The following points are general recommendations, which should be actively considered when deciding on a programme of monitoring.

- Pre-eminence should be given to robust physical monitoring as an indicator of a breach in the integrity of the isolator e.g. isolator pressure, pressure change across filters, leak testing, systematic visual examination, filter integrity, air velocity, all in comparison with set limits.

- Microbiological monitoring of the isolator used for product preparation under Section 10 should be carried out every session until full confidence is established in the system and the process. This would normally not be less than 10 satisfactory consecutive sessions.
  The decision to reduce from this level should be made locally between Q.A and Production staff.

- If a reduced level of monitoring is considered acceptable then this reduction should be carried out gradually. An example of this is;

  Every session - 1 session/day - 2 sessions/week - 1 session/week

  Monitoring one session per week is considered the minimum requirement provided no problems are encountered.

  The Table gives a typical monitoring sample level for Isolators used to compound medicinal products.

Isolator/Device	**Number of Samples**		
	Settle Plates	Surface Sample	Finger Dabs
Isolator <1.5m (2 glove)	2	2	1 pair
Isolator >1.5m (4 glove)	2	2	2 pairs

- Large batch production of products with substantial expiry dates (e.g. where environmental results would be known before release) should continue to be monitored for each session.

- Regular (e.g. weekly) monitoring of warehouse/storage/transfer isolators is recommended.

- Agar plates used with VHP processing must be validated to check that peroxide does not enter the plates and impair recovery of microbes. After monitoring with contact plates the area should be thoroughly cleaned using a validated cleaning procedure. Active air sampling and particle counts within the compounding isolator are an additional requirement at a minimum frequency of three months.

Evaluation of monitoring results

Results of monitoring which show microbial contamination may not only be indicative of ingress of micro-organisms through the integrity of the isolator(s) but may also indicate a failure of the VHP biodecontamination process. Therefore such results need to be taken more seriously than contamination found in a spray/wipe disinfected isolator and components where the spray / wipe process is not considered to be a surface sterilant.

Section 9.5.7.2.4 of the PIC's document on Isolators states that "The detection of any micro-organisms from environmental monitoring inside the isolator should be considered as requiring a full scale investigation.

Consideration should be given to the wisdom of releasing product still in house and the continued use of the isolator may not be appropriate".

Bibliography

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