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Guidance Note No. 1

Assurance of Sterility for container closure in-direct product contact surfaces in Aseptic process filling.
Role of vaporised hydrogen peroxide bio-decontamination in a contamination control strategy combining Sterilisation + Bio-burden control + VHP/vH_2O_2

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Ensuring sterility of indirect product contacting surfaces

This article is the first in a series of PHSS guidance notes prepared by industry subject matter experts and sterile product manufacturing specialists to facilitate understanding and interpretation of aspects of GMP guidelines for aseptic manufacturing of sterile medicinal products. The initial focus of this guidance is on the assurance of sterility of surfaces that contact product contacting parts e.g. product container closures/ stoppers, associated vibratory feeder bowls, hoppers and chute/ trackway surfaces.

Container Closure Vibrating Feeder Bowls and Hoppers

Introduction

Sterility must be assured for both direct product contact surfaces and for surfaces that contact these product-contacting parts – presenting an indirect route of contamination transfer to sterile products. Assurance of sterility requires application of a qualified sterilisation process that delivers overkill levels of efficacy, together with contamination control in aseptic process operator interactions during manufacturing of sterile medicinal products. Correct application of GMP technical and operational contamination control measures is essential.

A risk-based contamination control strategy (CCS) is mandatory in GMP and together with application of quality risk management (QRM) principles it is recommended to combine a recognised sterilisation process. This should comprise of out-of-place e.g. moist heat or dry heat sterilisation with a VHP®/vH_2O_2 bio-decontamination in-place for indirect product contact surfaces e.g. stopper contact surfaces.

The focus of this guidance is not assurance of sterility for direct product contact parts in aseptic manufacturing, where sterilised surfaces should only be exposed to Grade A environments inside barrier systems (Isolators or Restricted Access Barrier Systems [RABS]). However, due consideration should be given to associated closed transfer methods and protection via uni-directional airflow in Grade A environments. For example, product contact pre-sterilised filling needles and associated product tubing should only be exposed for aseptic process filling under Grade A conditions inside the barrier system zone. Entry to the Grade A zone should be via a closed transfer method with entry only after a qualified VHP®/vH_2O_2 bio-decontamination cycle when Grade A conditions are established. After entry into the barrier system protective uni-directional airflow at Grade A conditions provide a suitable environment for aseptic processing. Alternatively, a product pathway with clean-in-place (CIP) and sterilise-in-place (SIP) of the filling needles may be applied in a barrier system, but only after completion of a VHP®/vH_2O_2 cycle.

Examining the relative limitations and advantages of hydrogen peroxide vapor in aseptic processing – considering surface bio-decontamination where zero CFU recovery is required inside Grade A environments

This guidance considers the strengths and limitations of VHP®/vH_2O_2 relative to the penetration limitations and impact on efficacy of high or protected bio-burden on indirect product contact surfaces. Guidance includes requirements for contamination/bioburden control after application of a qualified sterilisation process. Bioburden control is required through subsequent steriliser offload, transfer and staging in a Grade C surrounding environment of an Isolator barrier system together with aseptic assembly into place before final closed barrier VHP®/vH_2O_2 bio-decontamination in advance of aseptic processing.

Vibrating container closure feeder bowls, hoppers and guide chutes within an aseptic processing Isolator cannot be sterilised in place by a recognised sterilisation process.

VHP®/vH_2O_2 is not a recognised sterilisation process (not fully penetrative) and is therefore not suitable as a sole method of assuring sterility within an Isolator barrier system.

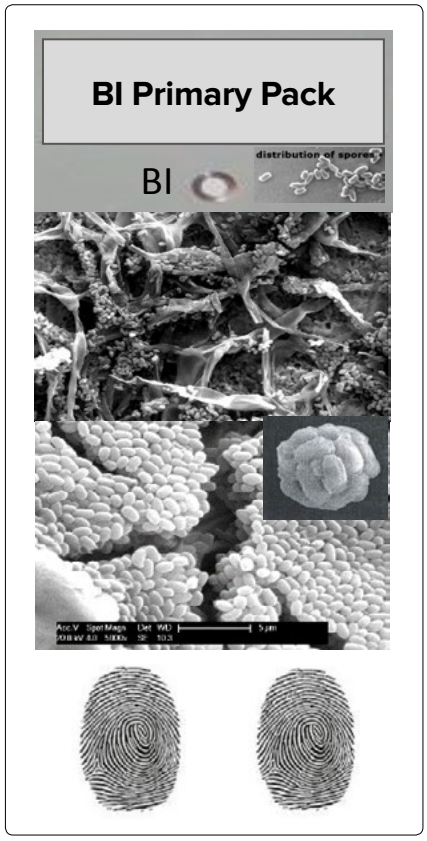
For aseptic process filling within an Isolator to provide the necessary assurance of sterility for stopper contact surfaces a contamination control strategy is required that combines an out-of-place sterilisation step, in-process transfers with bioburden control and a final in-place VHP®/vH_2O_2 cycle.

Procedural in-process transfer steps require contamination risk mitigation. Handling of sterilised and wrapped equipment would include staging in a Grade C cleanroom and aseptic assembly into the Isolator barrier as a final set-up step through an open barrier door before the closed barrier VHP®/vH_2O_2 cycle.

Considering the following evidence, it is demonstrable that Biological indicator (BI) inactivation at 6log sporicidal overkill levels of efficacy via a VHP®/vH_2O_2 bio-decontamination process applied in a barrier technology Isolator cannot act as a proxy to assure surface sterility of indirect product contact surfaces adjacent to the BI.

It has been shown that although BIs with a well distributed monolayer of spores may be inactivated at over 6log sporicidal reduction levels, and in principle surface sterilisation may be claimed, adjacent contaminated surfaces that are unsuitable for penetration of VHP®/vH_2O_2 are not necessarily rendered sterile – hence invalidating any claims of surface sterility.

So-called Rogue BIs with mass spore layers, spore clumps or contaminated BIs that demonstrate unexpected positive growth in a qualified VHP®/vH_2O_2 cycle demonstrate the penetration limitations of VHP®/vH_2O_2 and emphasise the importance of pre-cleaning surfaces (protective soiling removal) and pre-cycle bioburden control.



Although qualification studies with no growth of Geo Bacillus stearothermophilus spore BIs in TSB media incubated at 55-60°C for a 7-day duration together with extrapolations from a death kinetics survivor curve of 12 log sporicidal reduction indicates sterilisation conditions have been reached in the sample tested, adjacent surfaces may not be sterile.

One important consideration is that indirect product contact surfaces should be suitable for a surface bio-decontamination treatment process based on gas or vapor application e.g. non-porous surfaces that do not occlude microorganisms in a porous matrix-structure, with very low bioburden and without mass microbial clumping that VHP®/vH_2O_2 cannot or has limitations to fully penetrate. Additionally, ensure no possible protective contaminants like fatty acids from human skin contact that can occlude VHP®/vH_2O_2 from effective bio-decontamination.

Claiming VHP®/vH_2O_2 as a sterilisation process based on inactivation of BIs with well distributed spores without an understanding of the limitations of VHP®/vH_2O_2 has been challenged in GMP compliance as a fragile process and can lead to failure to meet QRM principles where process, science and risk knowledge are required.

Other considerations where enzyme indicators (EIs) are proposed as a proxy for biological indicators would require correlation studies between BIs and EIs for a given process, to provide comparability data that demonstrates EI efficacy and inherent variability are comparable or better than BIs. However, VHP®/vH_2O_2 'fragility' is about the limitations and robustness of the process to bio-decontaminate mass or protected contaminants of process equipment surfaces and not just about the challenges in qualification of VHP®/vH_2O_2 cycle efficacy via studies using challenge indicators, whether BIs or EIs.

Due consideration must be given to the penetration limitations of VHP®/vH_2O_2 in bio-decontamination of indirect product contact surfaces of processing equipment e.g. stopper transport pathways, that are required to be sterile and free from CFU recovery in Grade A zones.

During aseptic processing transfers of out-of-place sterilised wrapped parts through Grade C areas and associated in-place assembly set-up operations it essential to consider sterile wrapped surfaces may be at risk of bio-contamination through in-process transfer steps and associated handling procedures.

Bio-contamination may in turn be protected by subsequent process soiling which can act as a barrier to hydrogen peroxide vapor efficacy e.g. fatty acids from skin contact, including gloved hands touching skin then contacting surfaces.

In addition, poor set-up of loads e.g. with surfaces touching each (creating occluded surfaces) would prevent exposure to VHP®/vH_2O_2 and together these risks impact overall efficacy and robustness of the bio-contamination control status.

Load hanging point contact support hooks that are free to move in set-up procedures are not considered as suitable for good contamination risk management, as operator error could result in load surfaces touching each other resulting in post VHP®/vH_2O_2 cycle bio-contamination on occluded surfaces and then contamination spread via gloved operator handling in the Isolator Grade A zone. Adjustable hooks must be fixed after set up so that load items do not accidentally touch.

Vaporised molecules of hydrogen peroxide can be delivered to target volumes for exposure and to target surfaces in different environmental control system configurations. Application for surface bio-decontamination can be achieved in different ways to achieve process lethality where the oxidising potential and free radical attack mechanisms apply. Hydrogen peroxide molecules are generated by flash evaporation at Pico 10^{-12} size that can pass through HEPA filter media and Tyvek® primary packaging of biological indicators in variance to dry fog aerosol droplets that are produced by pressurising a liquid

disinfectant through a nozzle (micron size) that cannot pass directly through filter medias – so not all processes that apply H_2O_2 are equal or comparable.

VHP®/vH_2O_2 is a condensable vapor and not a true gas with flash evaporated molecules subject to hydrogen bonding that can impact gas-molecule distribution, thus water molecules in the environment at cycle start can be a barrier to vH_2O_2 molecule distribution via inherent localised bonding or incoming molecules being attracted to preferential sites where surface condensate layers have formed.

For processes that achieve saturated vapor conditions, past dew point, the formation of H_2O_2 deposition layers (typically 2–6 micron is adequate for 6log+ sporicidal reduction on surfaces) provides a dynamic process with constant exchange of molecules from the surface to gas volume.

The dynamic molecule exchange of VHP®/vH_2O_2 maintains efficacy on surfaces over a qualified cycle phase time and varies from disinfection processes that apply a static layer of disinfectant for a contact time where other factors of varying modes of action and possible residues will need consideration.

The greatest strengths of VHP®/vH_2O_2 are its broad spectrum efficacy, its sporicidal efficacy and that it also inactivates viruses; plus, that it is safely broken down to components of oxygen and water. This means it is environmentally friendly with easy to remove gas residuals via dilution or catalytic filter cells. Such an agent also complies with biocide directive regulations making it a widely applied bio-decontamination process with years of development knowledge and GMP compliance history in the pharmaceutical industry.

Once the limitations are understood VHP®/ vH_2O_2 can be applied to many applications in the pharmaceutical industry including: material transfers, barrier system bio-decontamination, indirect product contact surfaces bio-decontamination and room gaseous disinfection.

It is important to understand the science behind the bio-decontamination process applied in GMP aseptic processing applications. Not all processes are the same and may be impacted by different process variables, with specific limitations that need to be understood and risks managed via control measures. Deviations from the specified control conditions via inherent and process variability during process operations should be characterised to enable overkill and detectability to be applied for robust bio contamination control.

The qualified VHP®/vH_2O_2 cycle used to render surfaces free of CFU recovery in a Grade A aseptic processing environment after a sterilisation process e.g. moist heat-autoclaving or dry heat sterilisation/ transfer/ staging/ aseptic assembly process into an Isolator should be justified via a risk based approach with consideration to science, process integration, impact from process variables, inherent contamination penetration limitations of VHP®/vH_2O_2 and surface exposure for bio-decontamination.

Bio-contamination risks and risk mitigation for assurance of sterility of indirect product contacting surfaces enclosed in an aseptic processing Isolator

The transfer of wrapped moist or dry-heat sterilised parts through cleanrooms to a Grade C cleanroom where an Isolator barrier is installed with continued handling through set-up assembly into the Isolator with an open barrier door aseptic assembly procedure is not without contamination risks, so risk mitigation is required.

Without the assurance that product contact sterilised surfaces e.g. inside a feeder bowl or chute transport surfaces remain sterile through all handling/ transfer steps it is necessary that VHP®/vH_2O_2 is applied as a final complementary bio-decontamination step with 6log sporicidal activity. Such a step provides an overkill relative to low levels of bio-burden to render surfaces free of CFU recovery inside the Grade A controlled aseptic processing environment.

Target surfaces should be exposed to the full process lethality of the qualified VHP®/vH_2O_2 cycle; it is recommended any Tyvek®/ bio-barrier covering used to protect sterilised surfaces in transfer and assembly through an open barrier door should be removed before the VHP®/vH_2O_2 cycle.

Also, with the hydrogen bonding characteristics of VHP®/vH_2O_2 molecules once inside (under) the Tyvek® cover, full aeration will be compromised in removing bonded molecules and deposition layers through the filter media.

The removal of the protective covering through the open barrier door should be the final set-up step before the barrier door is closed and the VHP®/vH_2O_2 cycle is run.

Contamination risk mitigation measures, technical and procedural, would be required as soon as the protective covering is removed to exclude as far as possible extraneous contamination on sterilised surfaces. Unavoidable bio-contamination before the VHP®/vH_2O_2 cycle should be maintained at very low levels of bioburden to assure process lethality is not compromised and post-VHP®/vH_2O_2 cycle indirect product contact surfaces are free of CFU recovery.

Such protective bio-shield/ bio-barrier packaging can also create particle generation in handling

to reduce size for waste removal through closed transfer pathways e.g. Rapid transfer α-β port so the recommended practice is to remove the covering via an open barrier door where subsequent compression of the packaging for waste handling is outside the Grade A environment.

Once the protective Tyvek® covering is removed via the open Isolator barrier door the sterilised surfaces are open to contamination exposure (both particle and microbial) so the barrier door should be immediately closed after protective covering removal as a pre-VHP/vH_2O_2 cycle set-up step.

Contamination risk mitigation steps are required to protect as far as possible sterilised surfaces and maintain unavoidable extraneous bioburden, as a result of handling procedures, at an extremely low level before the pre-aseptic processing VHP®/vH_2O_2 cycle: PHSS guidance suggests;

- Less than 10 CFU bio-burden and without a typical microflora.
- Elimination of protective contaminants through good handling practices and good aseptic technique.

Typical microflora should be characterised in qualification studies and trended through environmental monitoring.

Contamination risk mitigation steps for the aseptic assembly procedure on installation of wrapped sterilised indirect product contact parts into the Isolator barrier are recommended as:

- Additional gowning: mask and eye covering (or full face covering) and sterile Tyvek® long sleeves to slip-on over grade C gowning to reduce risks of bioburden contamination into the Isolator Grade A zone during open barrier door set-up procedures.
- At each entry into the open barrier door during aseptic assembly set-up procedures gloved hands should be applied with a disinfectant to control bio-burden and extraneous contamination.

  After the barrier door is closed for the VHP®/vH_2O_2 cycle additional gowning applied in set-up of the Isolators can be removed and gowning reverted to that required for Grade C cleanrooms and Isolator aseptic processing operations.
- Isolator down-flow uni-directional airflow in operation with open-door outward flow to surround. Airflow should be characterised by visualisation studies to verify protective attributes are provided.
- Door access control, only barrier door(s) that is/are defined for the procedure are open.
- Bioburden characterisation and qualification studies are completed on indirect product contact sterilised surfaces to verify less than 10 CFU bioburden before the VHP®/vH_2O_2 cycle. Any bioburden comprises typical microflora in the cleanroom transfer pathway from the steriliser.

The operation of the Isolator HVAC Air-flow management systems to provide protective air during open barrier door set-up procedures will require a software configuration to disable pressure alarms when the barrier door is open.

If more than one barrier door is required to be open during the set-up procedure protective (out-flow) airflow characterization studies should cover open doors or alternatively doors opened in sequence, reflecting the normal/ worst-case operating procedure.

Case study part 1: (not mandatory) the following recommended process steps should be applied for assurance of sterility of indirect product contact surfaces of container closure transport systems: Feeder bowls, hoppers, chutes, trackways.

For a given application QRM would apply together with specifying assurance of sterility control measures in an associated contamination control strategy (CCS).

1. Clean indirect product contact parts out-of-place, ideally using an automated cleaning process.
2. Autoclave/ moist heat or dry heat sterilise container closure contact surfaces e.g. stopper feed surfaces in protective wrapping e.g. Tyvek® coverings for moist heat sterilisation. The moist heat sterilisation cycle should result in dry surfaces after the full sterilisation cycle. The applied protective covering should as a minimum cover the surfaces that should be sterile in aseptic processing operations e.g. inside of feeder bowl, chute container closure transfer surfaces.

   Applied coverings should allow in-place mechanical assembly/ fixing to process machines inside the Isolator Grade A zone without full protective covering removal until all the set-up assembly procedures are completed. Such wrapping may include a bowl ‘bonnet’ and over-wrap.

If the sterilised-wrapped parts hold or staging time in the Grade C area or in-process transfer paths require movements through a number of areas with extended pathways there is a greater risk of contamination and further risk mitigation should be considered. It may be necessary to consider double wrapping of parts for moist heat-autoclave or dry heat sterilisation with the secondary wrapping removed after hold/staging and before the primary wrapped/covered parts are assembled into the Isolator (pre-VHP®/vH_2O_2 cycle set-up procedure).

3. Transfer sterilised/ wrapped equipment to the Grade C cleanroom where the Isolator is installed. The transfer path, time and any hold conditions or staging time (pre-entry to Isolator) should be qualified so that sterilised parts remain protected as far as possible from extraneous contamination.

   Staging/ holding of wrapped-sterilised parts should not be at floor level or in areas where contamination levels put the items at risk of extraneous contamination.

4. Assemble single wrapped/ covered sterilised parts into the Isolator onto the process machine with an open barrier door(s) intervention and apply contamination risk mitigation control measures.

5. At the last open barrier door set-up procedure remove the primary Tyvek®/ protective coverings through the open barrier door and close the barrier door ready for a VHP®/vH_2O_2 cycle.

6. Operate a qualified and repeatable 6log+ overkill sporicidal VHP®/vH_2O_2 bio-decontamination cycle with aeration to target cycle endpoint (typically less than 1ppm if processing biological products that are highly sensitive to free radical attack and oxidation at low levels of gaseous residuals) as an automatic bio-decontamination cycle with cycle/ batch record.

7. Respect Isolator 'First air' principles and good aseptic technique in barrier aseptic process operations without any barrier glove contact to surfaces that have requirements of assured sterility – both product contacting parts e.g. filling needles, containers closures and in-direct product contact surfaces e.g. Container closure transport surfaces etc.

   During aseptic processing barrier operations if barrier gloves come into contact with direct or indirect product contact surfaces the event should be reported, documented and assessed with appropriate actions taken relative to contamination risks and product impact.

Product contact surfaces including product fluid path and filling needles should be subjected to a recognised and qualified sterilisation process and only exposed to Grade A aseptic processing environments e.g. after a subsequent qualified VHP®/vH_2O_2 bio-decontamination cycle.

Sterilised parts such as single-use filling needles should only be introduced into the Grade A controlled environment after the completion of a valid VHP®/vH_2O_2 cycle.

Non-product contact surfaces of process machinery inside the Grade A zone of the Isolator, including outside surfaces of stopper bowls, are bio-decontaminated together with the internal Isolator barrier surfaces and indirect product contact parts via an automated VHP®/vH_2O_2 bio-decontamination cycle qualified to meet greater than 6log sporicidal efficacy.

For non-product contact surfaces pre-VHP®/vH_2O_2 cycle bioburden control is applied as a function of pre-cleaning. Such surfaces do not need assurance of sterility in transfer or during set-up and assembly procedures, but as the surfaces are to be enclosed in the Grade A environment during aseptic processing any environmental monitoring surface sampling should result in zero (0) CFU recovery.

Case study part 2: Recommended contamination risk mitigation steps for bioburden control before operation of a VHP®/vH_2O_2 cycle

Bioburden should be characterised and controlled throughout the in-process transfer and aseptic assembly steps. Before the VHP®/vH_2O_2 cycle is operated and directly after the Tyvek®/ protective covering is removed, and barrier door(s) closed bioburden studies should be completed on the container closure contact surfaces e.g. inside surfaces of stopper bowl, on trackways and chute (upper) transport surfaces.

1. The Isolator HVAC; Airflow management system delivering uni-directional down-flow air at velocities around 0.45 m/s (± 20%) should be active during the open barrier door intervention. Pressure control alarms need disabling during the open-door intervention with airflow operational. Outward airflow from the open barrier door to the surrounding Grade C cleanroom should be qualified and maintained during the inherent set-up intervention aseptic assembly procedure.

2. Barrier doors should have access control, with open doors recorded during aseptic processing set-up operations. Only the door(s) that are required to complete the qualified aseptic assembly process should be opened to carry out the procedure.

3. For the open barrier door aseptic assembly procedure additional gowning should be applied including (but not limited to);
   - Face mask, beard covering, goggles or full face covering
   - Long disposable sterile Tyvek® sleeves or change to full suit (Tyvek® or re-useable).

4. Hand-Glove disinfection procedures should be applied at each entry into the open barrier door Grade A zone during the aseptic assembly set-up steps before the closed barrier VHP®/vH_2O_2 cycle.

5. The open barrier door assembly procedure should follow good aseptic technique practices to minimise the risk of bioburden contamination transfer that may compromise assurance of sterility of the container closure indirect product contact surfaces.

Recommended application of this guidance

This guidance applies only to Aseptic processing Isolator operations with VHP®/vH_2O_2 bio-decontamination and with a surrounding environment for the Isolator of Grade C.

RABS: Restricted Access Barrier systems used in aseptic process filling are subject to separate guidance with contamination risk mitigation and risk control measures applied relative to contamination risks in a Grade B surrounding area, but in principle the following applies:

Open design RABS may be specified and qualified with manual disinfection of the RABS barrier and non-product contact surfaces of enclosed process equipment where VHP®/vH_2O_2 is not applied.

In this case the surrounding environment is required to be Grade B for GMP compliance and sterility assurance is applied via out-of-place sterilisation processes for direct and indirect product contact parts. Assurance of sterility is maintained through qualified open-door set-up operator interventions including contamination risk mitigation and control measures. Such operator interventions should be the subject of study to verify contamination control measures are effective in process simulation trials and media fills.

Closed design RABS that employ VHP®/vH_2O_2 bio-decontamination of the RABS barrier and enclosed process equipment would also require a Grade B surrounding environment hence bioburden is already low. In this case QRM can be applied with VHP®/vH_2O_2 bio-decontamination of indirect product contact parts as a sole method to achieve surface conditions with zero CFU recovery, if risks are higher with sterilisation out-of-place and transfers through Grade C/B areas into place. Such an approach must be justified, risk assessed and defined in the contamination control strategy.

Not all Closed design RABS employ VHP®/vH_2O_2 bio-decontamination and in these cases the same requirements as Open design RABS apply.

Considering Quality risk management RABS should be operated as a closed operation with no open-door barrier operator interventions after the last bio-decontamination step inside the barrier and through aseptic processing. Any justified and risk assessed open-door interventions should be rare and subjected to qualification studies in process simulation trials for example PSTs and Media fills.

PHSS guidance is not mandatory but represents a consensus view from the PHSS aseptic processing and bio-contamination special interest group on good manufacturing practice and has been reviewed by the MHRA before publication from a regulatory compliance perspective. However, MHRA would point out that the user should not try to implement this guidance without a proper application of knowledge and true understanding of the science behind the strengths and weaknesses of VHP®/vH_2O_2. Each case will be reviewed on its own merits and early engagement with your regulator is strongly encouraged.

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