



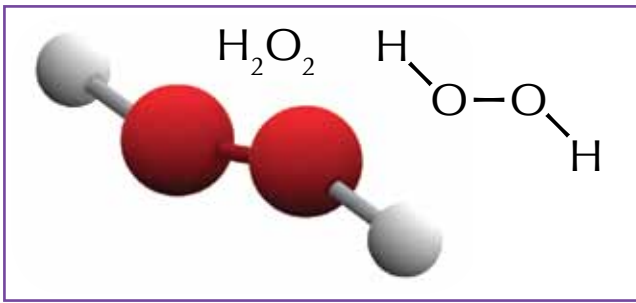
## Improving efficiency in bio-contamination control and risk mitigation using H<sub>2</sub>O<sub>2</sub> decontamination processes

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PHSS Chairman (2010) – Pharmaceutical & Healthcare Sciences Society.

There is a need to improve the efficiency in the pharmaceutical industry to meet new challenges of globalisation, competitiveness and the increasing diversity of products. The risk of biological contamination is increasing and, unchecked, is a risk factor for production processes and product quality, with potentially damaging consequences on business performance and risks to patient health.

This white paper considers environmental monitoring and contamination control strategies using the benchmark hydrogen peroxide vapour (HPV) gaseous bio-decontamination process. Using best practice and the latest technology, significant efficiency savings can be identified at different process stages.

## Bio-contamination control and monitoring. Key element of aseptic process risk management



### Bio-contamination control and monitoring

**Quality Risk Management (QRM) needs to consider the inefficiencies in microbiological monitoring. The forthcoming revisions to the ISO14698 standard on bio-contamination in cleanrooms and controlled areas and the USP<1116> microbiological control and monitoring of aseptic processing environment chapter, will place more emphasis on 'contamination rates'.**

Conventional bio-decontamination of cleanrooms and support areas involves manual processes using suspension test-validated disinfectant agents. However, these agents are not generally validated in-situ with industry standard biological challenges. This makes it difficult to verify any log reductions in bioburden following the bio-decontamination process.

Additionally, the lack of a process for the controlled removal of the disinfectant agent residue can result in ongoing material damage. Without active removal, surfaces can be left 'wetted' with aggressive, high efficacy, high concentration, broad spectrum sporicidal agents.

There may also be increased resistance to low efficacy disinfectants, providing the need to use rotated agents including the periodic use of a general sporicidal agent.

Sampling to identify the bio-burden contamination levels can also be fraught with errors. There can be poor recovery rates, and samples may only represent a fraction of the actual environment and operational time. There is also an increasing awareness that a significant percentage of the bio-burden may be viable but non-culturable organisms. These may have been subject to environmental and nutritional stress at the time of monitoring. It should be recognised that environmental monitoring results of zero cfu do not necessarily mean absence of contamination; it merely means that the bio-burden was below the level of detection at the monitoring location and at the point of sampling. Contamination is unlikely to be homogeneously distributed.

Without qualification, conventional bio-decontamination processes, typically called sanitisation, require significant environmental monitoring to measure the impact on bio-contamination control. Such processes and monitoring strategies, using 'Alert' and 'Action' levels, are now under review. These reviews are challenging the efficiency to control and detect bio-contamination for contamination risk reduction.

### Improving bio-decontamination assurance

As monitoring technology improves, the detection of 'actual' contamination will present new challenges. Improvements in monitoring need to be complemented by improvements in bio-decontamination control. Alongside this, 'decontamination assurance' needs to be demonstrated through log reductions in the biological contamination to pre-defined target levels.

Scientifically, it is impossible to demonstrate a cleanroom or controlled environment is 'sterile', a term that has a simple definition, but is complex in application within pharmaceutical and biopharmaceutical manufacturing environments.

However, if an environment is characterised in terms of microbiological profile and contamination rates under operational conditions, then this control state can be monitored for excursion. The key is achieving and identifying a characterised control state that presents an acceptable risk of bio-contamination.



*Bioquell Clarus® HPV generator hooked up to a large filling line.*

Hydrogen peroxide vapour (HPV) decontamination technology, originally used in isolator barriers, has developed a wider application. It is used in Restricted Access Barrier Systems (RABS) and in cleanroom/controlled areas.

It is likely that as microbiological monitoring technology develops with improved recovery rates, rapid, or 'real-time' detection, then excursions from current 'Alert levels' will result in far more 'excursion data' and increased investigations than previously recorded. More evidence and detectability of 'actual' contamination will present a new challenge in risk reduction.

### Bio-decontamination efficacy and material/process compatibility

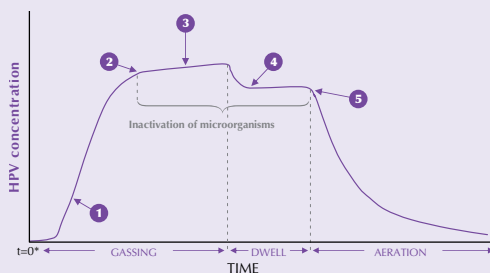
The level of biological decontamination is specified in terms of sporicidal log reduction. Typically 6-log for critical areas/surfaces and 4-log for surrounding environments. Decontamination assurance is provided by processes based on sound science, with automated control and monitoring of critical control points.

The HPV process can be validated with *Geobacillus stearothermophilus* biological indicators<sup>1</sup> to routinely achieve 6-log sporicidal reduction at room scale. Biological indicators are an industry standard method used to validate steam sterilisers/autoclaves. The gaseous vapour phase decontamination process<sup>2</sup>, using hydrogen peroxide under specified conditions, has been accepted by international regulators as a method of achieving 'surface sterilisation'. Most importantly the HPV process is not 'wet' when compared with manual disinfection. In the optimised process<sup>3</sup> vaporised hydrogen peroxide molecules are only delivered to surfaces past dew point<sup>4</sup>, at a sub-visible and effective level (2-6µm thickness) and controlled removal leaves surfaces residue-free. The contact time of the active HPV (at sub-visible 2-6µm thickness), and the residue-free nature following the aeration cycle, separates the process from a 'wet' condition. HPV also exhibits broad material compatibility and can be successfully used in areas containing sensitive electronics.



HPV can decontaminate complex work areas housing sensitive electronics.

## Hydrogen peroxide vapour (HPV) technology



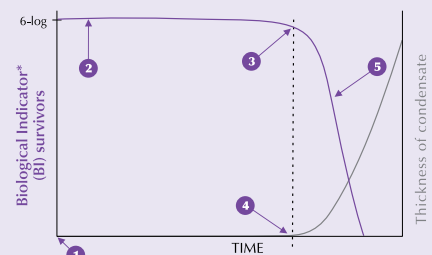
\* Conditioning phase not shown (vaporiser reaches temperature)  
Note: 'features' on graph change e.g. depending on size of chamber (& related temperature effect)

### Schematic of Bioquell HPV concentration/time graph

1. HPV introduced - initial rapid increase in HPV concentration
2. HPV saturation/'dew point' achieved – onset of rapid bio-decontamination
3. HPV gassing plateau – sustained micro-condensation effecting bio-deactivation
4. Dwell period (contact time)
5. Aeration – removal of HPV from the atmosphere typically by catalytic conversion to water vapour and oxygen, leaving no residues

### Schematic of dew point and Bioquell kill dynamics

1. Injection of HPV into the enclosure starts (t=0)
2. Only slight decline in biological indicator population prior to dew point
3. Rapid micro-biological kill occurs immediately after saturation/'dew point' is achieved – process optimised to achieve reliable 6-log sporicidal reduction on all exposed surfaces
4. Onset of micro-condensation correlates with rapid bio-deactivation
5. Bio-deactivation achieved via micro-condensation (invisible layer) of hydrogen peroxide (2-6µm)



\* Typical BI: Tyvek® pouched 6-log *Geobacillus stearothermophilus* spores

In cleanroom facilities, a rare 'oxygen bubble' effect can sometimes be observed. Some poor quality painted or coated surfaces that are porous and have a low bond to the substrate, allow hydrogen peroxide to pass through. With the breakdown in contact between the surface and the substrate, oxygen bubbles lift the surface coating.

This is not a chemical attack and such poor quality surfaces should have no place in a pharmaceutical facility. However, if 'lifting' is found to occur, proper 'bonded coat' repairs are required. This issue is easy to manage and any negative effect is far outweighed by the advantages of a thorough and measurable bio-decontamination process.

For more details on hydrogen peroxide vapour systems, call +44(0)1264 835 835 or email [info@bioquell.com](mailto:info@bioquell.com).

## Potential efficiency savings using a HPV bio-decontamination process

By improving bio-decontamination assurance using a scientifically robust process that is validated for repeated and high efficacy, the following applications can yield significant efficiency saving:

1. Using the HPV bio-decontamination process, filling lines can be gassed-in-place (GIP), including indirect product contact parts such as feeder bowls. This strategy presents significant efficiency savings and risk reduction<sup>5</sup> over traditional autoclaving out-of-place, followed by aseptic transfer and assembly.
2. Following commissioning after facility shutdown, or re-qualification, recalibration, cleanrooms can be returned to 'microbiological control' state quickly, by deploying the HPV process which can be verified using a biological challenge. This process can be deployed as a bio-decontamination service without the need for capital expenditure.
3. At the restart of a HVAC 'set back' in a cleanroom facility following a quiet or non-operational period, validated HPV decontamination process can provide evidence for compliance, enabling the room to be returned quickly into production.
4. Traditional 'spray and wipe' disinfection transfers for materials entering cleanrooms are now under challenge. The process is difficult to comprehensively validate. With an increasing use of pre-packaged sterile consumables now entering cleanrooms, more thorough and repeatable bio-decontamination processes are required. This has led to significant growth in high efficiency, HPV 'gassed' transfer chamber products. These provide a more effective and fully validatable bio-decontamination process. The efficiency saving represents a significant reduction of investigations into contamination ingress, and cross contamination, as a result of compromised in-process transfers.

## Discussion

The HPV process provides a more 'complete' bio-decontamination. When a high efficacy, automated bio-decontamination process is used (including in-process critical control point monitoring), significantly less microbiological monitoring is justified, limiting sample sites to worst case and high risk locations. The reduction in monitoring reduces the cost and extent of monitoring, in addition to reducing the risk of false positives.

***By improving the 'decontamination assurance' using a scientifically validated HPV process, there will be an inherent improvement in 'sterility assurance'.***

## References

1. PDA Technical Report No.51 (Dec 2010), Biological Indicators for Gas and Vapor-Phase Decontamination Processes: Specification, Manufacture, Control and Use
2. Pharmaceutical & Healthcare Sciences Society – PHSS RABS White paper, Sept 2010, including MHRA, FDA review. info@phss.demon.uk
3. Beatriz Unger-Bimczok et al – J Pham Innov (2008) 3;123-133
4. Watling et al PDA Journal 2002 Vol 56 No.6
5. Drinkwater – Impact of QRM on RABS - Cleanroom Technology December 2010

Disclaimer: Bioquell UK Ltd or its affiliates, distributors, agents or licensees (together 'Bioquell') recommends that customers ensure that the requisite level of bio-decontamination is achieved using standard biological indicators such as 6-log *Geobacillus stearothermophilus* spores; and the Bioquell technologies, subject to appropriate cycle development, are designed to be able to provide such levels of bio-deactivation.

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For further information on Bioquell's technology including an up-to-date listing of the scientific papers supporting the effectiveness of Bioquell technology in the life sciences setting, or to arrange an initial consultation:

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