A Two Part study to investigate the Environmental (viable) and Physical impact on Pharmaceutical Cleanrooms when High Efficiency Particulate Air filtered supply is temporarily suspended.

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Introduction

The manufacture of sterile pharmaceutical products must be conducted in dedicated cleanroom facilities, maintained and operated in line with EU GMP parameters[1]. The Heating Ventilation and Air Conditioning (HVAC) system controls supply and extract of High-efficiency particulate (filtered) air, which is essential for maintaining regulatory requirements.

Approximately 50% of a pharmaceutical cleanrooms total energy is dedicated to continuously running a HVAC system[2]; however, 78% of a HVAC systems operating time is for maintaining cleanroom parameters, when no operational activities are being undertaken.

In October 2020, the NHS launched its campaign for a greener NHS with a net zero emission target by 2040[3]. Energy prices are set to increases which means the cost of running a HVAC system will increase two fold, during a time of austerity.

This two part study was conducted to ascertain the risk and impact of switching off the HVAC system to the cleanroom environment, to enable HVAC switch off out of working hours, as both a cost reduction and carbon neutral strategy.

Methods

Sampling methods adopted are shown in figure 1, and were conducted in line with ISO14644[4] and EU GMP[1]

Figure 5 – Sampling methods adopted for study 1 and 2. Physical monitoring only conducted during study 1.

Study 1 sampling parameters for the viable and particulate impact of operator presence during supply disruption are shown in figure 2.

Figure 6 – Sampling protocol adopted for study 1

Study 2 sampling parameters for the viable and particulate impact of operator presence during supply disruption are shown in figure 3.

Method	Working Parameters	0-30 minutes	30-90 minutes	90-120 minutes
1	Operative processes undertaken	HVAC Operating	HVAC Operating	HVAC Operating
2	Unoccupied	HVAC Operating	HVAC "Switched Off"	HVAC Operating
3	Operative processes undertaken	HVAC Operating	HVAC "Switched Off"	HVAC Operating

Figure 7 – Sampling protocol adopted for study 2

Both studies were conducted in a fully operational cleanroom suite consisting of C and D grade cleanrooms.

Results – Study 1

Physical Parameters

No impact on the cleanroom physical parameters
✓All within EU GMP limits[1] and storage requirements

Airborne particle concentration

As shown in figure 4, there was significant variation 5µm particle concentration; skew in favour of post HVAC switch off.

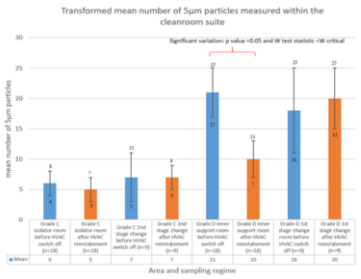

Figure 1 – Graph showing 5µm particle concentration measured in study 1.

Viable recovery

Significant variation found during Active Air Sampling, again a skew in favour of post HVAC switch off, this is shown in figure 5.

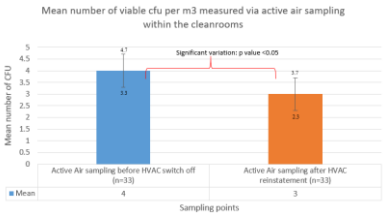

Figure 2 – Graph representing the viable cfu recovered during active AAS in study 1.

As shown in figure 6, there was significant variation in viable recovery from surface samples, this time higher recovery post HVAC switch off

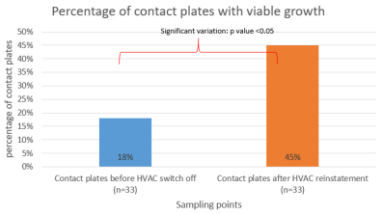

Figure 3 – Graph representing the viable cfu recovered during surface sampling in study 1

Viable recovery Genus identification – ***figure 7***

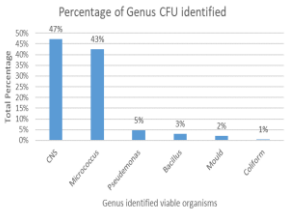

Figure 4 – graph depicting % of genus identified microbes

- Low recovery rates
- No notable difference in genus identification before and after HVAC switch off

- Genus identification conferred with trends and types of cleanroom microflora identified in a study conducted by Sandle in 2011[5]
- The presence of these micro-organisms in our cleanrooms:
  - Cleaning activities
  - Changing rooms
  - **Ultimately personnel shedding**

✓ All results from study 1 within particle concentrations and viable counts were within EU GMP limits

Results – Study 2

Airborne particle concentration

As demonstrated in figure 8 and 9, significant variation for both 0.5µm and 5µm particle concentration was found, when staff are working within the cleanroom and HVAC is switched off.

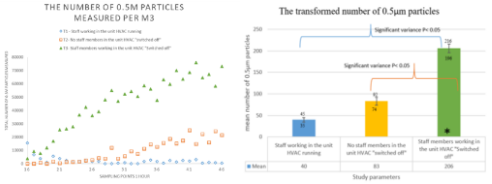

Figure 8 – Graphical representation of 0.5µm particle concentration during the three study parameters of study 2

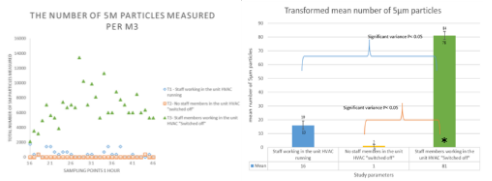

Figure 9 - Graphical representation of 5µm particle concentration during the three study parameters of study 2

Viable recovery

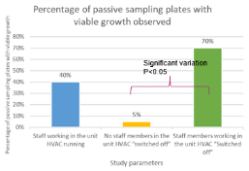

Figure 10 – graphical representation of the % of viable passive sampling recovery during study 2.

Recovery rates for viable growth was low; however, significant variation found with viable growth detected between test 2 and test 3, as shown in figure 10.

Conclusion

- There is **no** significant variation in the working parameters of the cleanroom following 12 hour HVAC system "switch off"
- Operators **do** significantly affect the environmental parameters of a cleanroom when a HVAC system is "switched off".
- Operators **are** the biggest risk to our cleanrooms.
- Removal of operators prior to HVAC "switch off" and restriction of re-entry post HVAC reinstatement, is **key** to ensuring surfaces are free from viable bioburden and minimal risk to pharmaceutical products.

Further Studies and Recommendations

- HVAC "Switch off" for a period of 12 hours out of operational hours, can be safely adopted with no significant impact of physical and environmental conditions on reinstatement.
- If HVAC switch off is adopted, trend analysis of viable growth recovered must be completed for a minimum of three months to ensure no long term effect on the background bioburden
- Additional thought should be directed on the risk to cleanrooms following an unexpected HVAC failure during operational hours.
- The findings of this study are of national significance and through a risk based approach, could be applied to other NHS Pharmaceutical aseptic unit.

References

[1] Medicines and Healthcare products Regulatory Agency (MHRA), 2022. Annex 1. 11th ed. London: Pharmaceutical Press.
[2]Tschudi, W. & Xu, T., 2001. Cleanroom Energy Benchmarking Results, California: University of California.
[3] NHS England, 2022. Delivering a 'Net Zero' National Health Service, London: NHS England and Improvement.
[4] International Organization for Standardization, 2005. ISO14644 Cleanrooms and associated controlled environments - Part 3: Test methods, Geneva: ISO.
[5] Sandle, T., 2018. The human microbiome and the implications for cleanroom control. European Journal of Parenteral and Pharmaceutical Science, 23(3), pp. 89-98.