Validation of a sporicidal bio-decontamination process for use in pharmaceutical isolators in an NHS aseptic manufacturing unit

Brian McBride QA Dept Pharmacy Altnagelvin Hospital, Derry, Northern Ireland (Brian.McBride@Westerntrust.hscni.net)

Introduction and aims

The recently published revision of EU GMP Annex 1 Manufacture of Sterile Medicinal Products includes a requirement for pharmaceutical isolators to undergo a bio-decontamination process of the interior which should be automated, validated and controlled within defined cycle parameters and include a sporicidal agent. It is widely accepted that the easiest way to achieve this is by converting Hydrogen Peroxide (H_2O_2) liquid into a state that will diffuse readily through the closed isolator chamber leading to bio-decontamination of all surfaces which it comes into contact with.

There is a range of bio-decontamination systems on the market from Devea (www.devea-environnement.com)which are claimed to be suitable for use in hospital pharmacy clean room facilities. One model from this range, the Phileas Genius is a simple, stand-alone battery powered unit that generates vapourized hydrogen peroxide of particle size 5-10 µm from 7.4% solution using novel spinning disc technology. This generator can be transferred into and out of any closed isolator work zone through the transfer hatch (as long as the hatch door is wide enough) and can be used to do pre-programmed cycles (called zones) to routinely decontaminate inner surfaces.

The aim of this study is to validate this Phileas Genius hydrogen peroxide bio-decontamination process for use in pharmaceutical isolators in a hospital aseptic manufacturing unit operating under an MHRA Specials manufacturing licence. The accepted standard for validation of this type is demonstrating 6 spore Log Reduction (SLR) using Geobacillus stearothermophillus impregnated disc Biological Indicators (BI) placed throughout the isolator chamber.

Specifically the validation needs to show:

1. The H_2O_2 solution used in the process is able to produce a H_2O_2 vapour that is effective at achieving 6 spore log reduction inside the isolator.
2. The preprogramed parameters in the generator 'zones' (volume of H_2O_2 liquid diffused per cycle, delay time between diffusion cycles and contact time) are sufficient for decontamination and that there is a suitable margin for safety from the point at which the cycle would be sub lethal.
3. There is diffusion of H_2O_2 throughout the isolator work zone to give assurance all internal surfaces of the critical work zone are in contact with the H_2O_2.

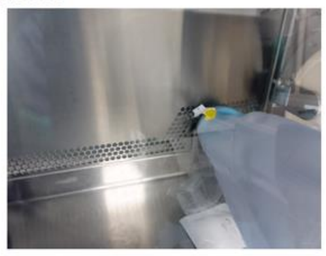
Method

1. Devea recommended parameters for a suitable decontamination cycle to be programmed into the Genius. These were based on the isolator internal volume.
2. The decontamination cycle was validated by carry out 3 proving runs in one of the MAT isolators in the aseptic unit.
3. For each proving run Geobacillus Stearothermophilus BI were placed in 7 positions throughout the isolator to allow exposure to the H_2O_2 mist created by the Genius.
4. After exposure for the correct contact time the BI were transferred aseptically into sterile TSB
5. The TSB was incubated at 55 degrees for 7 days and viewed for the presence or absence of growth.

Fig 1 BI and Phileas generator positions for validation

Top LHS- Isolator with open glass visor. Phileas in the centre

Top RHS- BI at the glove end of the sleeve



Bottom LHS -BI in the hatch and lower corners (Front and rear)

Bottom RHS- BI in upper corner (Front and rear) and on hanging bar

Results (Table 1 2x proving cycles)

Isolator 8	Date: 26/08/22	Cycle parameters:7.5% H2O2 X 6 with 5minute interval. Max 3h contact time			
Position		Date:30/08/22	Date:01/09/22	Date:02/09/22 (day 7)	+ve inoculation @ day 7 read 05/09/22
Hatch 1 and 2		--	--	--	++
Lower front (glass) 1 and 2		--	--	--	++
Upper back (panel) 1 and 2		--	--	--	++
Glove sleeve 1 and 2		--	--	--	++
Lower back (panel)		--	--	--	++
Upper front (glass) 1 and 2		--	--	--	++
Bar middle 1 and 2		--	--	--	++
Contact time 1h Contact time 2h		- -	- -	- -	++ ++
Positive control		+	+	+	

(Table 2 1x proving cycle)

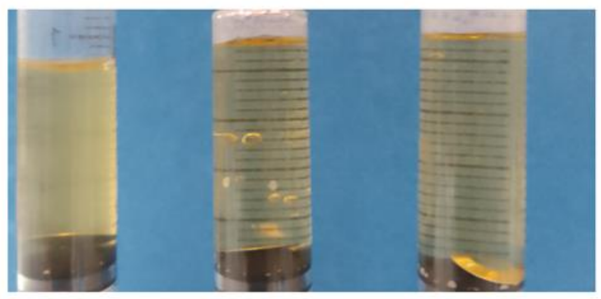
Isolator	Date: 01/09/22	Cycle parameters: 7.5% H2O2 X 6 with 5minute interval. Max 3h contact time			
Position		Date:05/09/22	Date:07/09/22	Date:9/09/22	+ve inoculation @ day 12 read 16/09
Hatch		-	-	-	+
Front glass lower		-	-	-	+
Front glass upper		-	-	-	+
Back panel lower		-	-	-	+
Back panel upper		-	-	-	+
Glove sleeve		-	-	-	+
Bar LHS		-	-	-	+
Bar RHS		-	-	-	+
1h dwell		-	-	-	+
2h dwell		-	-	-	+

Fig 2 Broth following 7 days incubation

1- Broth is cloudy. Indicates viable Geobacillus stearothermophilus

2- Broth is clear. Indicates 6 Log reduction

3- Broth is clear. Indicates 6 Log reduction



Results

After 7 days incubation at 55 degrees the TSB for the BI at all the positions in the isolators remained clear. This indicates 6 Log reduction in the Geobacillus spores on the disc.

Discussion

The results from the proving runs indicates successful validation of the decontamination system.

These show that the process produces a H_2O_2 mist in the isolator that is effective at achieving 6 Log kill of Geobacillus and as this is accepted as an industry standard should also be effective against other microorganisms.

They also prove that the decontamination cycle parameters advised by Devea are suitable and have an additional safety margin shown by achieving 6 Log reduction with the shorter exposure time. It may be possible to further optimise the cycle to reduce its length to a minimum but this would require additional validation.

The isolator used for the validation (MAT) is representative of a typical pharmaceutical isolator used in NHS aseptic units. As all the BI positioned throughout the chamber experienced 6 Log reduction it is reasonable to assume all internal surfaces exposed to the mist would be suitably decontaminated. Areas at risk of not coming into contact with the mist included the gloves/ gauntlets and the area of the isolator base that the Genius sits on during the cycle. Procedures need to be put in place to remove this risk.

Conclusions

The aseptic unit in which this work was done operates under MHRA Specials Manufacturing authorisation. It is the intention that this system and process will be presented at the next inspection as an attempt to comply with the requirement in revised Annex 1 for sporicidal decontamination. The inspector who carried out the previous inspection has indicated the MHRA would be happy with the approach used in this validation and it will be examined in detail at the next inspection.

The unit is completing a programme of isolator replacement and this includes sucessful validation of the system in the new isolators (different manufacturer from the existing isolators). This has been found to be an advantage of the system over the integrated systems currently on the market.

Declaration of interest

The equipment used was purchased from AB Scientific UK www.abscientific.com

AB scientific and Devea both provided technical advice and assistance and made no financial contribution to the work.

References

USP, Supplement 1, <1229.11>, "Vapor Phase Sterilization" USP 38 (US Pharmacopeial Convention, Rockville, MD, 2015)