Advanced Therapy Treatment Centres

Northern Alliance Advanced Therapies Treatment Centre

Recommendations in the design and execution of a study to evaluate the impact of sporicidal disinfection during ATMP manufacture

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Introduction

During aseptic manufacture of medicines, it is necessary to transfer starting materials from an uncontrolled environment into the critical processing environment (critical zone). For aseptic manufacture, the critical zone must meet GMP Grade A conditions, one of the criteria for this is the absence of viable microorganisms on the surfaces and air within that environment.

Effective transfer disinfection of components and starting materials into an aseptic environment is a critical process when performing aseptic manufacture of pharmaceuticals. Whilst this process was historically performed with 'spray and wipe' techniques utilising 70% alcohol as the disinfectant solution, developments in technology, disinfectants, and regulatory expectations have seen the introduction of various sporicidal processes to achieve greater assurance in the transfer process. Currently, automated or manual processes are available which utilise chemical surface decontamination using chemical agents in order to kill any microorganisms present on the surfaces of materials transferred into the critical zone.

The choice of decontamination method, and the agents used to achieve disinfection must not have a detrimental impact on the items which are exposed to them during the disinfection process. The Guidance for Specials Manufacturers[1] included an exemption "for the manufacture of radiopharmaceuticals and biologics only where evidence is available that the product performance may be affected by sporicidal residues. Justification may be possible for other medicines however documentation to support the approach taken should be available."

In recognition of the above, this paper has been compiled to describe a potential method for obtaining sufficient data to justify the omission of the sporicidal step where is it demonstrated to be detrimental to viable cells subjected to the disinfection process employed.

Sporicides are specifically designed to disrupt and damage cellular material, it is reasonable to deduce, therefore, that any exposure of cellular starting materials to sporicides has the potential to adversely affect the quality of the cells to which they are exposed.

It should also be acknowledged by industry when considering commercial ATMP presentations, it will be necessary to perform surface disinfection of the product where a preparation step is required at, for example, a treatment site pharmacy. NHS guidance requires the use of a sporicidal agent during transfer disinfection unless the exemption can be applied. This should be taken into account when the final container for a cellular product is chosen.

[1] MHRA, 2021. Guidance for Specials Manufacturers. [Online]
Available at: https://www.gov.uk/government/publications/guidance-for-specials-manufacturers

Potential for Exposure

Application of sporicidal agents disinfection processes can be achieved via either automated 'gassing' cycles, or manually using either a spray directly onto the item being disinfected, or wiping the item with a pre-impregnated sporicidal wipe. In any scenario, the sporicidal agent is transferred to the item and remains in contact with the surface for a minimum of the required contact period depending on the method employed. During this contact time, there is potential for migration or permeation of the disinfectant agent through the surfaces of the containers being disinfected to a greater or lesser extent depending on the materials of construction. Cellular products may be at greater risk due to the common requirement for some containers to be semi-permeable.

The potential damage that results to the biological material may be as a result of sporicidal residues permeating through the container, or inadvertently remaining within the fluid pathway or product contact surfaces, after the disinfection process, and contacting cells during manufacture, leading to cell damage or death. A thorough understanding of the process and potential for exposure is required. A structured risk assessment would help to determine the highest risk steps and determine the components or containers which should be included in any study on sporicide residues. All potential containers and materials should be considered in the risk assessment (e.g. different apheresis bags).

In order to obtain evidence of the potential exposure, studies may be performed which establish the likely levels of exposure using the components or containers indicated from risk assessment. Studies may be designed by exposing a container filled with a surrogate product to the sporicide, or simulated processing of a surrogate product using components sanitised using the sporicide. In either method, it will be necessary to allow for inherent variation in different factors by, for example, extending the sporicide exposure time in order to assess the worst case scenario. Other factors should also be considered which have been identified in the risk assessment such as additive effects of transfer through various components.

Following the simulation process, the concentrations of sporicide in the surrogate product can be established. In order to be able to draw meaningful conclusions from the data, the principles of method validation contained in ICH Q2 (International conference on harmonisation, quality guideline 2) should be applied. In particular, LoQ (Limit of Quantification), LoD (Limit of Detection), range and linearity of any method employed must be appropriately demonstrated.

The analytical methods listed below are some options available which may be useful depending on the sporicide in use, and potential route of exposure:

- (U)HPLC-MS (Ultra) (High Performance Liquid Chromatography)
- ICP-MS (Induction Coupled Plasma - Mass Spectrometry)
- ICP-OES (Induction Coupled Plasma – Optical Omission Spectrometer)
- Conductivity
- pH
- TOC (Total Organic Chemistry)

When designing a study, inclusion of appropriate controls such as negative controls should be considered.

Impact of Exposure

Following execution of the study, where residue has been identified in the surrogate product, it is then necessary to determine the impact of that residue. Where no sporicide residue is identified, the impact of sporicide at the LoD must be established.

The final stage of the assessment process would involve exposing biological material of the type being manufactured to sporicide at the concentration known to exist. This must be done in a controlled manner rather than relying on sporicide transfer during sanitisation. For example, addition of a quantity of sporicide to growth media during a validation batch.

Once the manufacturing process has been completed with sporicide exposure, the product must be analysed to identify the impact of such exposure. There should already be established biological analytical methods which can be employed for this purpose, the methods chosen must establish if the presence of the sporicide has been detrimental to the product during manufacture.
All of the steps described above should be documented in a formal protocol, including acceptance criteria on the final biological analysis. The protocol must be approved prior to execution.

Conclusions

Where it is established there no unacceptable detrimental impact of sporicidal disinfection, then it should routinely be employed as part of the transfer disinfection process.

Where detrimental effects are identified (e.g. reduction in cell counts, viability or function of cells) beyond that which can be accepted, the executed protocol may be used to support justification of omission of a sporicidal disinfection process.