Contamination Control Strategy

Regulatory bodies expect that pharmaceutical companies have a Contamination Control Strategy (CCS) in place that outlines the control of contamination of utilities, manufacturing systems and environment and ultimately the pharmaceutical product itself. The question is what are the key elements to be considered in order to meet the quality system requirements detailed in ICHQ10 in addition to ICHQ9 and EudraLex Volume 4 Annex 1 for a CCS? What points need to be considered to support the implementation of such a program within any manufacturing facility? What makes it robust? Should it be multifaceted to ensure its effectiveness?

These are all valid questions and key to ensure your CCS is robust. One important facet is that the strategy is to be built on a risk-based foundation. From the start, it requires a multidisciplinary team with a good understanding of the process, the utilities and equipment that serve the process. Cross-functional expertise allows scientific justified assessments to be made of potential microbiological, particulate, chemical and cross-product risk to your product. A solid CCS also provides an estimation for the likelihood of a risk occurring and severity of the impact to the patient if the risk occurred. This allows you to identify the key areas of focus in the CCS and provides rationale for implementation of control or detection measures.

Development of a robust plan is critical in all manufacturing facilities – aseptic, terminal sterilisation and non-sterile. This is not futility as pharmaceutical manufacturing generally comprises a complex, multi-step processing system in which significant risks from various types of contamination are presented by different sources. Clear regulatory guidance is available on the need for exclusion and control of contamination at all stages during manufacture, however, addressing contamination control in a non-sterile manufacturing environment is less clear cut. Under all circumstances, good knowledge of your own process is paramount.

A CCS is a not a stand-alone plan but more a summary of practices and measures that are interlinked. The sum of all these individual aspects and how well these interact determines the effectiveness of the CCS from the selection and management of raw materials to final packaging of the product. For example, how the material and personnel flows are designed, is there cleaning, sanitisation, and sporicidal treatment and how is the robustness of the controls monitored through the environmental monitoring programme and in process or finished product testing.

When controlling contamination of pharmaceutical raw materials, the primary aim is to exclude any contamination which may subsequently result in deterioration of the product or may harm the patient. If raw materials are not of the desired quality, they can be sources of contamination for your (intermediate) product. The origin and composition of the raw materials gives a good indication of whether the ingredient has the potential to be a source of contamination or can cause proliferation of microbial growth. Besides product contamination, raw materials have the potential to contaminate equipment and the manufacturing facility. This can lead to long term issues that are very difficult to eliminate and result in repeat contamination of product or cross contamination to other products. In particular, microbiological contamination poses a risk of biofilm formation or spore contamination that can be very difficult to remove.

Water is the most common used "raw material" within a pharmaceutical manufacturing process and different grades of pharmaceutical water are typically used for different processes. As water is used in many different applications, there is not only the direct risk of contamination of the product, but also indirectly as water can act as a vector for contamination causing transmission from one system to the other. The design of your company's water system augmented with a good preventive maintenance and sanitisation regime in combination with a sound monitoring program significantly contributes to microbial risk reduction.

One indispensable part of the CCS is environmental control in the cleanroom. Physical parameters such as relative humidity, temperature and differential pressures give an indication of the HVAC performance. In aseptic manufacturing environments air flow patterns are of significant importance in terms of transfer of contamination between areas. Your Environmental Monitoring (EM) programme needs to determine the types and level of microbial and non-viable particulate contamination present in the cleanroom. Sample locations must be selected through risk assessment. With an effective EM programme in place, analysis of the data collected can quickly verify that the cleaning and disinfection processes in place are effective and allow adverse trends to be quickly identified. EM is an important tool for determining the state of control of the facility and therefore, is an important part of the monitoring programme for all types of manufacturers.

As the number one source of contamination in controlled areas is personnel, training is key! The CCS must address personnel barriers to contamination whether the manufacturing process is designed for aseptic or non-sterile manufacturing facilities. The CCS should describe the rationale for the level of gowning chosen, the frequency of gown cleaning, behaviour of personnel in the controlled rooms and the acceptability of the gown materials for the type of manufacturing process. Personnel working in the area must rigidly adhere to the gowning procedures in place. Training should involve a practical element; it should be continuous and ongoing monitoring is an essential part of an effective CCS. Training should include

an initial and periodic assessment of gowning and until fully qualified, personnel access to the cleanroom should be restricted. A risk-based approach should be undertaken to assess frequency of retraining.

After personnel, the second highest risk of contamination is from materials and equipment brought into the controlled environment from the outside. For material transfer airlocks, it is essential that decontamination practices are in use prior to entry into the controlled environment. Items to be considered include the use of interlocking airlocks between entry points for classified areas of different grades, restricted and controlled access to aseptic areas through use of card readers etc., disinfection of materials to include use of a sporicidal where appropriate, sufficiently detailed material transfer procedures in an SOP and assessment of transfer techniques by an SME to validate compliance with your SOPs.

The frequency of your cleaning and disinfection programmes should be risk-based and similar to the training programme, should be regularly reviewed. Two disinfectants should be used in rotation, one being a broad-spectrum disinfectant rotated with periodic use of a sporicidal agent. Have you validated your disinfectant prior to use? This is also key to an effective CCS and should include surface challenge testing to calculate the log reduction of each microorganism tested with the disinfectant. The selected surfaces must be representative of those that are present in your facility. Besides the obligatory ATCC strains the microbial challenge panel must also include environmental isolates to demonstrate effectiveness. Other items to be considered under the cleaning and disinfection programme include the frequency and method for residue removal, performance of studies to demonstrate the ability to recover from loss of aseptic control and disinfectant efficacy studies to include contact times and expiry dating.

Consideration should also be given to identifying and defining your product contact surfaces and ensuring that in an aseptic process, these surfaces are sterilised and protected from contamination before, during and after processing. All wrapping materials in use must be of the appropriate quality to ensure a microbial barrier and low particle generation. The considerations in a non-sterile facility are similar as there needs to be proof that the sanitisation program used is effective and the frequency of use of sporicidal agents is appropriate and commensurate with the risk to the patient.

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