MICROBIAL RISK MANAGEMENT DURING CLEANROOM OPERATIONS

Overview

The Risk Management of Contamination (RMC) system is a systematic approach to the management of contamination. The system identifies microbial risks to a product, assesses the extent of the risk and where necessary, reduces it. The identified risks, or their methods of control, are monitored and limits established to ensure that contamination is correctly controlled. The system is then verified on a continuing basis to ensure that it is working effectively. Associated documentation and training requirements are also an important stage of this system.

When a knowledge and understanding of the areas of greatest risk associated with the manufacturing process has been achieved, resource and cost can then be focused upon managing these areas, optimising the security and productivity of the process. For the manufacture or processing of sterile pharmaceutical products, the requirements for managing microbial contamination are prescribed in the regulatory documents published by both the European Commission and the US FDA. These documents include microbial concentrations that should not be exceeded, and methods to minimise the contamination of products. To achieve the requirements, risk management techniques are recommended by the regulatory authorities. Typically, a cleanroom is utilised for such products and is likely to incorporate critical zones or workstations, such as microbiological safety cabinets, isolators or restrictive access barrier systems (RABS) were product may be exposed and the RMC system considers aseptic manufacturing within such a cleanroom. However, the mechanisms of microbial contamination are also applicable to inert particle contamination and the method detailed in the last stage of the RMC method, and may be used to assess the microbial risk in other types of healthcare cleanrooms, such as those used for the manufacture of terminally sterilised and non-sterile products, and medical device products.

Risk Management Systems for Cleanroom Operations

Fault Tree Analysis (FTA), Failure Mode and Effect Analysis (FMEA), Hazard and Operational Studies (HAZOP) and Hazard Analysis and Critical Control Point (HACCP) are established systems used to control risks during manufacturing. The first three systems originate from the electrical, mechanical and petrochemical manufacturing industries, but can be used in cleanroom manufacture to manage activities such as safety, reliability, and validation. However, the HACCP system was developed for use in the food industry and can be more readily adapted to the control of contamination during cleanroom activities as it uses familiar principles and also considers control and monitoring methods. The HACCP system is the basis of the contamination control system used in ISO 14698-1 and offers a systematic way of assessing, controlling, and monitoring risk from contamination. This system has the following seven principles:

1. Conduct a hazard analysis
2. Determine the critical control points (CCPs)
3. Establish critical limit(s)
4. Establish a system to monitor control of the CCP
5. Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control
6. Establish procedures for verification to confirm that the HACCP system is working effectively
7. Establish documentation concerning all procedures and records appropriate to these principles and their application

This system requires interpretation and adaptation in order to be more readily applicable to cleanroom operations and this has been done to provide the RMC approach to the management of contamination.

Overview

Risk Management of Contamination (RMC) System

The RMC approach to cleanroom contamination control has been adapted from the HACCP method and provides an effective system to manage the risk from the various sources of microbial contamination during cleanroom manufacturing. It consists of the following seven stages:

1. Identification of the sources of contamination and routes of transfer to the product
2. Assessment of the risk from the sources and routes of contamination and, where appropriate, introduce new control methods, or improve existing control methods, to reduce risk
3. Establishment of a monitoring schedule using valid sampling methods to monitor the hazards, or their control methods, or both. Establishment of alert and action levels with procedures to be followed when these levels are exceeded
4. Verification, on a scheduled basis, that the contamination control system is appropriate by reviewing the product contamination rate, the environmental monitoring results, the risk assessment and control methods and the action levels, and where appropriate, modify accordingly
5. Establishment and maintenance of appropriate documentation
6. Training of the personnel
7. Determine the microbial risk to the patient from the product

The risk assessment stage is usually the most difficult stage to undertake but is a major component in the overall risk management process, and calculates the level of risk associated with a contamination source that then needs to be controlled. This assessment indicates where effort and resource should be best applied and so it is essential that the assessment is accurate. An assessment based upon the fundamental method of contamination transfer will provide the most accurate method as it utilises the actual contamination process. This approach is therefore appropriate for aseptic manufacturing processes and is used for the risk assessment stage. The risk to a patient, resulting from a contaminated product, is dependent on the likelihood of a micro-organism being present after manufacture and the chance of growth during the shelf life. This chance can be calculated by a method detailed in the last stage of the RMC method, and may be used to determine the level of control required during the associated manufacturing process.
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Who Should Attend

The course is suitable for all personnel involved in the management and operation of cleanrooms including Production Managers and Supervisors, Quality Assurance, Microbiologists, Sterility Assurance Specialists and Sterility Assurance Engineers.

Course Objectives

- Delegates will be able to identify the sources of contamination, routes of transfer to the product and contamination control measures and apply this in their facility.
- The course will provide a scientific assessment of the fundamental mechanism of contamination transfer, via surface contact or from airborne deposition, and how this mechanism is used to provide the most accurate methods of assessing risk of microbial contamination of product.
- Delegates will recognise how the identified risks, or their methods of control can be monitored and limits set to ensure that contamination is adequately controlled are outlined.
- Delegates will recognise the advantages of using a quantitative system to assess and prioritise risk based on actual process data.
- Methods of periodic verification that the contamination system is under control will be presented.
- Delegates will participate in risk assessment workshops lead by industry experts to enhance learning and facilitate debate.
- Methodology will be presented to determine the microbial risk to patient from aseptically prepared products.

Course Programme

Day 1

09:00 - 09:15 Introductions and Workshop Expectations

09:15 - 09:45 Risk Management of Contamination (RMC) during Cleanroom Manufacture, choice of Microbial Risk Assessment Method and Fundamental Mechanism of Contamination Transfer

09:45 - 10:30 Identification of Sources of Contamination, Transfer Routes, Key Control Measures and the use of Risk Diagrams (Group Exercise 1: Cleanroom Contamination Sources)

10:30 - 10:45 Tea/Coffee

10:45 - 11:45 Identification of Sources of Contamination, Transfer Routes, Key Control Measures and the use of Risk Diagrams (Group Exercise 2: Contamination Control Measures)

11:45 - 12:15 Level 1 Risk Assessments for General Cleanroom Areas

12:15 - 13:15 Lunch

13:15 - 14:15 Level 1 Risk Assessments for General Cleanroom Areas (Group Exercise 3: Quantification of General Cleanroom Risks)

14:15 - 15:00 Level 2 Risk Assessment for Aseptic Filling Processes

15:00 - 15:15 Tea/Coffee

15:15 - 16:15 Level 2 Risk System, Assessment of Manufacturing Stage Risks and Areas for Aseptic Improvement

16:15 - 16:30 Wrap up Day 1

Day 2

09:00 - 09:15 Review of Day 1

09:15 - 10:00 Level 3 Risk Assessments for Critical Area Contamination, Airborne Deposition (Group Exercise 5: Quantification of Contamination by Airborne Deposition)

10:00 - 10:30 Level 3 Risk Assessments for Critical Area Contamination, Surface Contact

10:30 - 11:00 Tea/Coffee

11:00 - 12:00 Level 3 Risk Assessments for Critical Area Contamination, Surface Contact (Group Exercise 6: Quantification of Contamination by Surface Contact)

12:00 - 12:30 Establishment of an Effective Monitoring Programme, Regular Verification of the Risk System, Documentation and Staff Training

12:30 - 13:30 Lunch

13:30 - 14:30 Assessing Microbial Risk to Patients from Aseptically Manufactured Products

14:30 - 15:00 Assessing Microbial Risk to Patients from Aseptically Manufactured Products (Group Exercise 7: Calculation of Risk to Patients)

15:00 - 15:30 Course Wrap Up Feedback and Questions

Course Notes and Certificates

Full course notes and a certificate of attendance will be issued to each delegate who attends the full course. Certification is for knowledge gained, not just attendance. Assessment for Aseptic Filling Process