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REVIEW ARTICLE

Risk Management of HVAC System in Pharma Industries

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ABSTRACT

Heating, ventilation, and air system encompasses heating, ventilation, and air conditioning, which is integral component of pharmaceutical facility functionality. The qualification of HVAC systems is done by using a risk based approach. The risk management program consists of four major components: risk assessment, risk control, risk review, and risk communication. All four components are essential. All the above methods should address the mentioned four basic components. Failure mode effect analysis (FMEA) concepts were used for risk assessment of a HVAC system to determine the scope and extent of qualification and validation in this present work. The HVAC is the "direct impact" system in the aseptic practice which directly affects the product quality and regulatory compliance. The level of risk associated with the HVAC system was assessed based on the impact and severity of the probable risk in aseptic practice in sterile manufacturing. After completion of the risk assessment the recommended actions were extended and verified against the qualification stages of the HVAC system. The various parameters to be evaluated for the validation of HVAC system include air flow pattern, air flow velocity, air changes per hour, filter leak test, particle count, viable monitoring, filter integrity test, pressure difference, recovery test for temperature and humidity, temperature and humidity uniformity, and fresh air determination. Validation of HVAC system involves systemized and assembled documents of functional specifications; design drawings, plans, and specifications; validation master plan; testing, adjusting, and balancing (TAB); and startup reports.

KEYWORDS

Risk Management Program, Failure Modes and Effects Analysis (FMEA), Pharmaceutical Industry, validation

INTRODUCTION

A Risk Management Program starts with identifying the possible risks associated with a product or with the process used to develop, manufacture, and distribute the product. An effective quality risk management ensures the high quality of drug product to the patient.

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The FDA'S Initiative on Risk Management Approach

The FDA defines a Risk Management as, a strategic safety program designed to decrease product risk by using one or more interventions or tools. The FDA proposes that the sponsor of every product submitted for approval considers how to minimize risks from the product's use. Risk management planning generally encompasses all efforts by a sponsor to minimize the risk from its product's use and may include product labeling, risk assessment,

pharmacovigilance, and special studies or interventions.

The FDA expects the Risk management to follow a basic process of:

1. Learning about and interpreting a product's benefits and risks,
2. Designing and implementing interventions to minimize a product's risks,
3. Evaluating interventions in light of new knowledge that is acquired over time, and
4. Revising interventions when appropriate.

Risk Management Methods

To make risk-based decisions, a systematic approach is essential. The ICH Q9 guideline, Quality Risk Management, provides a structure to initiate and follow a risk management process. The following methods widely used in the industry for risk management.

- Basic risk management facilitation methods (flowcharts, check sheets, etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

Failure Method Effects Analysis (FMEA)

It provides for an evaluation of potential failure modes for process and their likely effect outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce, or control the potential failure. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex process into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures, and the likely effects of these failures. Potential areas of use(s) FMEA can be used to appropriate risk and monitor the effectiveness of risk control activities. FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process.

Failure Mode, Effects and Criticality Analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a failure mode, effects and criticality analysis. FMECA can identify where additional preventive actions might be appropriate to minimize risks.

Fault Tree Analysis (FTA)

The FTA tool is an approach that assumes failure of the functionality of a product or process. This tool evaluates system failures one at a time but can combine multiple causes of failure by identifying casual chains. The results are represented pictorially in the form of a tree of fault modes.

Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive and preventive tool for assuring product quality, reliability, and safety. It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent and control the risk or adverse consequences of hazards due to design, development, production and use of products.

HACCP consists of the following seven steps:

- Conduct a hazard analysis and identify preventive measures for each step of the process
- Determine the critical control points
- Establish critical limit
- Establish a system to monitor the critical control points

- Establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control
- Establish system to verify that the HACCP system is working effectively
- Establish a record keeping system

Hazard Operating Analysis (HAZOP)

HAZOP is based on a theory that assumes that risks events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called guidewords. Guidewords are applied to relevant parameters to help identify potential deviations from normal use or design intentions; HAZOP often uses a team of people with expertise covering the design of the process or product and its application.

Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and event that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product, or system.

The tool consists of

- The identification of the possibilities that the risk event happens.
- The qualitative evaluation of the extent of possible injury or damage to health that could results.
- A relative ranking of the hazard using a combination of severity and likelihood of occurrence.
- The identification of possible remedial measures.

Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk.

The tool involves breaking down a basic risk question into as many components as needed factors involved in the risk. These factors are combined into a single relative risk score that can be used for ranking risks- "Filters" in the form of weighing factors or cut-off for risk scores can be used to scale or fit the risk ranking to management or policy objectives.

Supporting Statistical Tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision-making.

Control Charts

- Acceptance control charts
- Control charts with arithmetic average and warning limits
- Cumulative sum charts
- Weighted moving average

Failure Mode and Effect Analysis

- FMEA is a systematic method of identifying and preventing system, product and process problems before they occur.
- FMEA is focused on preventing problems enhancing safety and increasing customer satisfaction.

Types of FMEA are

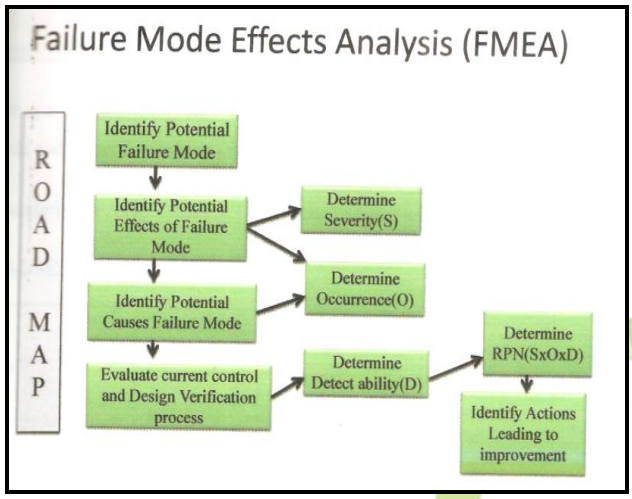
- System - focuses on global system functions
- Design - focuses on components and subsystems
- Process - focuses on manufacturing and assembly processes
- Service - focuses on service functions
- Software - focuses on software functions

Benefits of FMEA

FMEA is designed to assist the engineer improve the quality and reliability of design properly used the FMEA provides the engineer several benefits. Among others, these benefits include:

- Improve product/process reliability and quality

- Early identification and elimination of potential product/process failure modes
- Prioritize product/process deficiencies
- Emphasizes problem prevention
- Documents risk and actions taken to reduce risk
- Provide focus for improved testing and development



Failure Mode Effective Analysis Procedure

The process for conducting an FMEA is straightforward. The basic steps are outlined below.

- Describe the product/process and its function. An understanding of the product or process under consideration is important to have clearly articulated. This understanding simplifies the process of analysis by helping the engineer identify those product/process uses that fall within the intended function and which ones fall outside. It is important to consider both intentional and unintentional uses since product failure often ends in litigation, which can be costly and time consuming.
- Create a Block Diagram of the product or process. A block diagram of the product/process should be developed. This diagram shows major components or process steps as blocks connected together by lines that indicate how the components or steps are related. The diagram shows the logical relationships of components and establishes a structure around which the FMEA can be developed. Establish a Coding System to identify system elements. The block diagram should always be included with the FMEA form.

The FMEA Worksheet

Use the diagram prepared above to begin listing items or functions. If items are components, list them in a logical manner under their subsystem/assembly based on the block diagram.

Identify Failure Modes

A failure mode is defined as the manner in which a component, subsystem, system, process, etc. could potentially fail to meet the design intent. Examples of potential failure modes include:

Corrosion, Vibration, Foreign material, insufficient lubricant capacities, Temperature expansion, Inadequate Diameter, Inadequate maintenance instruction, Tolerance build up, Over load, Imbalance, Electrical Short or Open, Cracking

- A failure mode in one component can serve as the cause of a failure mode in another component. Each failure should be listed in technical terms. Failure modes should be listed for functions of each component or process step. At this point the failure mode should be identified whether or not the failure is likely to occur. Looking at similar products or processes and the failures that have been documented for them is an excellent starting point.
- Describe the effects of those failure modes. For each failure mode identified the engineer should determine what the ultimate effect will be. A failure effect is defined as the result of a failure mode on the function of the product/process as perceived by the customer. They should be described in terms of what the customer might see or experience should the identified failure mode occur. Keep in mind the internal as well as the external customer.

The FMEA worksheet

Component name	Function	Failure mode	Cause	Effect	Severity	Occurrence	Detection capability	RPN	Risk mitigation

- Establish a numerical ranking for the severity of the effect. A common industry standard scale uses 1 to represent no effect and 5 or 10 to indicate very severe with failure affecting system operation and safety without warning. The intent of the ranking is to help the analyst determine whether a failure would be a minor nuisance or a catastrophic occurrence to the customer. This enables the engineer to prioritize the failures and address the real big issues first.

Identify the causes for each failure mode. A failure cause is defined as a design weakness that may result in a failure. The potential causes for each failure mode should be identified and documented. Enter the Probability factor. A numerical weight should be assigned to each cause that indicates how likely that cause is (probability of the cause occurring). A common industry standard scale uses 1 to represent not likely and 5 or 10 to indicate inevitable.

Identify Current Controls (design or process). Current Controls (design or process) are the mechanisms that prevent the cause of the failure mode from occurring or which detect the failure before it reaches the Customer. The engineer should now identify testing, analysis, monitoring, and other techniques that can or have been used on the same or similar products/processes to detect failures. Each of these controls should be assessed to determine how well it is expected to identify or detect failure modes. After a new product or process has been in use previously undetected or unidentified failure modes may appear.

The FMEA should then be updated and plans made to address those failures to eliminate them from the product/process.

Determine the likelihood of Detection. Detection is an assessment of the likelihood that the Current Controls (design and process) will detect the Cause of the Failure Mode or the Failure Mode itself, thus preventing it from reaching the Customer. Based on the Current Controls, consider the likelihood of Detection using the following table for guidance. After ranking the severity, occurrence and detect ability the RPN can be easily calculated by multiplying these three numbers: RPN = S x 0 x D

This has to be done for the entire process and/or design. Once this is done it is easy to determine the areas of greatest concern. The failure modes that have the highest RPN should be given the highest priority for corrective action. This means it is not always the failure modes with the highest severity numbers that should be treated first. There could be less severe failures, but which occur more often and are less detectable.

Uses of FMEA

- Development of system requirements that minimize the likelihood of failures.
- Development of methods to design and test systems to ensure that the failures have been eliminated.
- Evaluation of the requirements of the customer to ensure that those do not give rise to potential failures.

- Identification of certain designs characteristics that contribute to failures, and minimize or eliminate those effects,
- Tracking and managing potential risks in the design. This helps avoid the same failures in future projects.
- Ensuring that any failure that could occur will not injure the customer or seriously impact a system.
- To produce world class quality products

Quality Risk Management in Pharmaceutical Production

QRM principles applied as a process supports science-based and practical decisions when integrated into commercial manufacturing. In general implementing QRM should not obviate a manufacturer's obligation to comply with regulatory expectations (example: regulatory requirements, regulatory filings, inspection commitments, etc.). All QRM activities should be structured in a way that allows escalation of risks to the appropriate management level within the organization. Special focus can be on the risk assessment and risk control of example

- product quality risks,
- adverse impact to patient health based on product quality defects,
- product supply interruption to patients,
- GMP and regulatory compliance risks,
- multisite risks,
- multiproduct risks,
- New facility and changes to existing facility, examples: start-ups, new commercial manufacturing processes, technology transfers and product discontinuation.

After completion of the risk assessment and risk control activities the outcomes must be summarized and communicated. The results may be documented in a new or existing report or they may be included as part of another document approved by appropriate decision-makers (example: site or functional management, system owner, quality unit, etc.). A risk review is important if new risks or changes to existing risk levels are identified through planned or unplanned events such as routine operation, changes, complaints, product returns, discrepancies/deviations, data monitoring, trends, inspections/audits, changes in regulatory environment, etc. Risk review may also include evaluation of example:

- effectiveness of risk control activities and actions;
- Changes in observed risk levels or existing controls.

Potential Areas for Risk Management Application

The following areas are identified as potential in the pharmaceutical industry for quality risk management application.

1. Documentation [SOPs, Batch records etc.]
2. Training [Schedules and effectiveness]
3. Quality defects [Complaints, deviations, OOS etc.]
4. Audits [Compliance]
5. Periodic reviews [Revalidation assessment]
6. Change controls [Impact assessment]
7. Development reports [Process and controls verification]
8. Facilities, Equipment and Utilities [Components, maintenance etc.]
9. Material management [Receipt, storage and distribution]
10. Packaging and labeling [Container closure system and labeling]

CONCLUSION

The risk management program consists of four major components: risk assessment, risk control, risk review, and risk communication. All four components are essential. All the above methods should address the mentioned four basic components. Team selection and method selection are also plays a vital role in the risk management process, so care should be taken while selection of risk management team and

method. FMEA is the preferable method for risk management in the pharmaceutical industry as FMEA analysis include higher reliability, better quality, increased safety and its contribution towards cost saving includes decreased development time and reduced waste and non-value added operations.

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