DOI: 10.55522/jmpas.v6i5.0148 ISSN NO. 2320 – 7418

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Review article

Risk assessment approach and its application in the pharmaceutical industry for product quality management

U K Singh* Shilpa Pahwa, Vandana Sethi

School of Pharmacy, Lloyd Institute of Management and Technology, Greater Noida, Uttar Pradesh, India

Corresponding author: U K Singh, ✉ upendra.singh81@gmail.com

School of Pharmacy, Lloyd Institute of Management and Technology, Greater Noida, Uttar Pradesh, India

Received – 20 August 2016**, Revised** - 25 September 2016, **Accepted** – 23 October 2017 **(DD-MM-YYYY)**

Refer This Article

U K Singh, Shilpa Pahwa, Vandana Sethi, 2017. Risk assessment approach and its application in the pharmaceutical industry for product quality management. Journal of medical pharmaceutical and allied sciences, V 6 - I 5, Pages -557 – 563. Doi: https://doi.org/10.55522/jmpas.V6I5.0148.

ABSTRACT

With the introduction of FDA's 21st century GMP and ICH initiatives (such as Q8 Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System), drug manufacturing entered a new era of risk management. Quality risk management is a process for assessment, control, communication and review of risk to the quality of the medicinal product. It can be applied both proactive and retrospectively. For any pharmaceutical product, Quality Risk Management shall be applied to aim that raising the level of protection for the patient by the reduction of the risk to which that patient is exposed at the time he /she receives a drug product. This general objective can only be achieved by implemented policy of quality risk management on the product and process design and its lifecycle. The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design.

Keywords: Quality risk management, Risk prioritization number.

INTRODUCTION

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 expects the Risk management to follow a basic process of

Learning about and interpreting a product's benefits and risks,

Designing and implementing interventions to minimize a product's risks,

Evaluating interventions in light of new knowledge that is acquired over time, and

Revising interventions when appropriate.

The guideline ICH Q9 provides a standard for quality risk management in the pharmaceutical industry. It explains what quality risk management is, how it can be applied to pharmaceuticals and how it can provide a common language with an agreed process for the pharmaceutical industry and regulators. The EU GMP guideline directly refers to ICH Q9. According to ICH Q9, pharmaceutical quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of a medicinal product across the product life cycle. 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. In addition quality risk management improves decision making if a quality problem arises. It should include systemic processes designated to co-ordinate, facilitate and improve science-based decision-making with respect to risk.

Quality risk management process

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. A model for quality

risk management is outlined in the diagram (Figure 1: Overview of a typical quality risk management process). The risk management program consists of four major components: risk assessment, risk control, risk communication, and risk review. 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.

The two primary principles of Quality Risk Management are

The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient and. The level of effort, formality and documentation of the Quality Risk Management process should be commensurate with the level of risk

Risk assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks. Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

Risk Identification: address what might go wrong.

Risk analysis, to analyse the risk involved.

Risk evaluation, comparing the risk identification and analyze the risk against the criteria.

Risk identification is the systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis and informed opinions. Risk identification addresses the “What might go wrong?” question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Examples of risk that may be identified include, but not limited to:

Risk to manufacturing equipment such as equipment downtime, equipment damage, cost of replacing equipment parts and any potential for injury.

Quality of the finished product.

Incorrect formulation composition.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk. The department subject expert shall analyze the operation and activity, discrepancies, deviations or failures and categorize the potential risk and its impact on the process or system or operation and/or product quality, yield, purity, potency, identity, stability, safety or efficacy.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions. After risk evaluation, risk has been categories as minor, moderate and high risk to design risk control

Minor Risk: This risk has low potential and is less likely to impact directly or indirectly the process, system, operation, product quality, yield, purity, potency, identity, stability, safety or efficacy.

Moderate Risk: This risk has moderate potential and is likely to moderately impact directly or indirectly the process, system, operation, product quality, yield, purity, potency, identity, stability, safety or efficacy.

High Risk: This risk has high potential and is likely to highly impact directly or indirectly the process, system, operation, product quality, yield, purity, potency, identity, stability, safety or efficacy

Risk Control

Risk control includes decision-making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions

Is the risk above an acceptable level?

What can be done to reduce or eliminate risks?

What is the appropriate balance among benefits, risks and resources?

Are new risks introduced as a result of the identified risks being controlled?

Examples of mitigation strategies that may be used to modify risk levels (RPN) are:

Modify process design such as additional data verification checks.

Introduce external procedures such as double-checking to counter possible Failures.

Increase the scope and level of testing applied during various stages of validation.

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of

other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows). Communications might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality.

Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions.

Risk management method and tools

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, Cause & Effect diagrams 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

Basic Risk Management Facilitation Methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision-making are:

Flowcharts;

Check Sheets;

Process Mapping;

Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram).

Failure Mode Effects Analysis (FMEA):

FMEA depends on product and process understanding. It methodically breaks down the analysis of complex processes into manageable steps. It provides an evaluation of potential failure modes for processes and their likely effect on product performance. It can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. This tool is further advanced with studying criticality of the consequences and providing clear indication of situation. The purpose, terminology and other details can vary according to type (e.g. Process FMEA, Design FMEA, Health FEMA etc.), the basic methodology is similar for all.

Failure Mode, Effects and Criticality Analysis (FMECA)

It is the extension of earlier said FMEA tool. Extending FEMA to incorporate an investigation of the degree of severity of consequences, their probabilities of occurrence and their detectability is failure mode, effects and criticality analysis. In FMECA, each failure mode of the product is identified and then evaluated for criticality. This criticality is then translated into a risk, and if this level of risk is not acceptable, corrective action must be taken. This can be utilized for failure and risk associated with manufacturing processes. The tool can also be used to establish and optimize maintenance plans for repairable systems and/or contribute to control plans and other quality assurance procedures. In addition, an FMEA or FMECA is often required to comply with safety and quality requirements, such as ISO 9001, QS 9000, ISO/TS 16949, Six Sigma, FDA Good Manufacturing Practices (GMPs), Process Safety Management Act (PSM), etc. When we perform a FMECA, we are identifying all potential failure modes and their associated effects. To make this task more manageable, we must first decide what type of FMECA we want to perform - Design,

Process, User, Software, Test, to name a few.

Fault tree analysis (FTA)

This tool assumes failure of the functionality of a product or process. The results are represented pictorially in the form of a tree of fault modes. This can be used to investigate complaints or deviation in order to fully understand their root cause and ensure that intended improvement will resolve the issues and not cause any other different problem.

Hazard Analysis and Critical Control Points (HACCP)

Hazard Analysis and Critical Control Points (HACCP) is a systematic, proactive and preventive tool for assuring quality, reliability and safety. It involves hazard analysis, determining critical control point, establishing critical limit, establishing a system to monitor critical control point and establishing a record-keeping system. This might be used to identify and manage risk associated with physical, chemical and biological hazards. It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the 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 limits;

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 Operability Analysis (HAZOP) HAZOP is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called "guide-words". "Guide-words" (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It 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 events 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 result and

A relative ranking of the hazard using a combination of severity and likelihood of occurrence, and

The identification of possible remedial measures.

Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking of risks. Risk ranking of complex systems typically requires the 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 to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs 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. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

Control Charts, for example:

Acceptance Control Charts;

Control Charts with Arithmetic Average and Limits;

Cumulative Sum Charts;

Shewhart Control Charts;

Weighted Moving Average.

Design of Experiments (DOE);

Histograms;

Pareto Charts;

Process Capability Analysis. Application of quality risk management in the pharmaceutical industry

Risk assessment is a valuable science-based process used in quality risk management (ICH Q9) that can aid in identifying which material attributes and process parameters potentially have an effect on product critical quality attibutes (CQAs). Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. The Risk Management Program shall cover the following areas, but not limited to:

Facilities and Equipment,

Production, processing and packing operations,

Quality Control Laboratories Testing

Materials warehousing and transportation,

Maintenance and Utilities,

Quality Assurance and Quality Management System,

Environment, Health and Safety, and any other area, considered significant for the risk for product quality, safety and efficacy.

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. Risk assessment tools can be used to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data. The initial list of potential parameters can be quite extensive, but can be modified and prioritised by further studies (e.g., through a combination of design of experiments and mechanistic models). The list can be refined further through experimentation to determine the significance of individual variables and potential interactions. Once the significant parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding.

Quality Risk Management and Product and Process Development

Quality risk management can be used at different stages during product and process development and manufacturing implementation. The assessments used to guide and justify development decisions, for example,

Risk analyses and functional relationships linking material attributes and process parameters to product CQAs.

Risk analyses linking the design of the manufacturing process to product quality.

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product;

To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options and process parameters;

To assess the critical attributes of raw materials, solvents,

Active Pharmaceutical Ingredient (API) starting materials, excipients, or packaging materials;

To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing);

To decrease variability of quality attributes:

Reduce product and material defects;

Reduce manufacturing defects.

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale-up and technology transfer;

Product Lifecycle Management and Continual Improvement

Throughout the product lifecycle, companies have opportunities to evaluate innovative approaches to improve product quality. Process performance can be monitored to ensure that it is working as anticipated to deliver product quality attributes as predicted by the design space. This monitoring could include trend analysis of the manufacturing process as additional experience is gained during routine manufacture. For certain design spaces using mathematical models, periodic maintenance could be useful to ensure the model's performance. Expansion, reduction or redefinition of the design space could be desired upon gaining additional process knowledge. Change of design space is subject to regional requirements.

Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system assures the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement. The process performance and product quality monitoring system should:

Use quality risk management to establish the control strategy. This can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. The control strategy should facilitate timely feedback / feed forward and appropriate corrective action and preventive action.

Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools);

Analyse parameters and attributes identified in the control strategy to verify continued operation within a state of control;

Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation.

Include feedback on product quality from both internal and external sources, e.g., complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings;

Provide knowledge to enhance process understanding, enrich the design space (where established), and enable innovative approaches to process validation.

Risk analysis methods applicable in the pharmaceutical industries

Preliminary Hazard Analysis (PHA) and Failure Mode and Effects Analysis (FMEA) methods are most frequently used at

different stages of product and process development for risk assessment.

Preliminary Hazard Analysis (PHA) The risk assessment in this development stage were qualitatively evaluated for developing the drug product, based on experience in the development of drug products, namely oral solid dosage and research data. Each hazard was rated by their severity and probability, and then classified into high risk (H), medium risk

(M) or low risk (L) according to the risk rating table shown in Table 3. Hazards with high risk or medium risk must be controlled as low risk by the control strategy from the drug product design.

Failure Mode and Effects Analysis (FMEA)

FMEA is the preferre 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.

The output of a risk assessment may be a combination of quantitative and qualitative estimation of risk. As part of FMEA, a risk score or Risk Prioritization Number or RPN may be assigned to the deviation or to the stage of the process that is affected; this helps to categorize the deviation. RPN is calculated by multiplying Probability (P), Detectability (D) and Severity (S), which are individually categorized and scored. The Risk Priority Number (RPN) methodology is a technique for analyzing the risk associated with potential problems identified during a Failure Mode and Effects Analysis (FMEA). There are presents a brief overview of the basic RPN method and then examines some additional and alternative ways to use RPN ratings to evaluate the risk associated with a product or process design and to prioritize problems for corrective action. FMEA can be performed to identify the potential failure modes for a product or process. The RPN method then requires the analysis to use past experience and judgment to rate each potential problem according to three rating scales:

Severity, which rates the severity of the potential effect of the failure.

Occurrence, which rates the likelihood that the failure will occur.

Detection, which rates the likelihood that the problem will be detected before it reaches the end-user/customer.

Rating scales usually range from 1 to 5 or from 1 to 10, with the higher number representing the higher seriousness or risk. For example, on a ten point Occurrence scale, 10 indicate that the failure is very likely to occur and is worse than 1, which indicates that the failure is very unlikely to occur. The specific rating descriptions and criteria are defined and analyzed to fit the products or processes.

After the ratings have been assigned, the RPN for each issue is calculated by multiplying Severity x Occurrence x Detection.

RPN = Severity x Occurrence x Detection The RPN value for each potential problem can then be used to compare the issues identified within the analysis. Typically, if the RPN falls within a pre-determined range, corrective action may be recommended or required to reduce the risk (i.e., to reduce the likelihood of occurrence,

increase the likelihood of prior detection or, if possible, reduce the severity of the failure effect). When using this risk assessment technique, it is important to remember that RPN ratings are relative to a particular analysis (performed with a common set of rating scales and an analysis team that strives to make consistent rating assignments for all issues identified within the analysis). Therefore, an RPN in one analysis is comparable to other RPNs in the same analysis but it may not be comparable to RPNs in another analysis.

FMEA process steps

The steps someone has to go through to design an FMEA form are described below:

Selection of the process. The importance of the process in terms of the impact of potential failures was taken into account as a selection criterion. Evaluation using FMEA works best on processes that do not have too many sub-processes.

Review of the process: The process was analysed and described in a flowchart and the process design was studied thoroughly for efficient output.

Brainstorm potential failure modes: Each stage of the process was studied and identified the ways it could potentially fail or the things that might go of wrong.

List of potential effects of each failure mode: List of the potential effects and their probable failure were prepared. Cause and Effects analysis (fishbone diagram) was used for this step.

Assign a severity rating for each effect: Each effect was given its own severity rating (from 1 to 10, with 10 being the most severe). To quantify or prioritize the effects, Pareto analysis was used.

Assign an occurrence rating for each failure mode: After collecting data on the factors responsible for the failure of the product, the failure frequency was determined and it were rated appropriately (from 1 to 10, with 10 being the most likely).

Assign a detection rating for each failure mode and effect: List of all controls currently in place to prevent each effect of a failure from occurring was prepared and a detection rating was assigned for each item (from 1 to 10, with 10 being a low likelihood of detection).

Calculation of the risk priority number (RPN) for each effect: RPN was calculated by multiplying the severity rating with that of occurrence rating by the detection rating.

Prioritize the failure modes for action: Depending upon the calculation and analysis carried out, the priority order was decided.

Taken action to eliminate or reduce the high-risk failure modes: The action to be taken for each high-risk failure was determined, and a person was assigned to implement the action /change.

SUMMARY

Tools for quality risk management can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products).The scientific approach used begins with identification of the desired dosage form and performance attributes through the target product profile. From this target product profile, an initial list of critical quality attributes was developed. A risk assessment was undertaken to identify the variables and unit operations which are most likely to impact the critical quality attributes. This was then used to focus development activities on potential high-risk areas. A risk assessment, starting with the physico-chemical characteristics of the API, led to the identification of a viable formulation and manufacturing approach. Formulation development involved the use of prior knowledge and structured experimentation to investigate the relationship between formulation component levels, API attributes and the drug product quality attributes. Development of the manufacturing process focused on the unit operations posing the greatest potential risk to drug product quality [1]. [8, 9].

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