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Implementation of Quality Risk Management (QRM) In Pharmaceutical Manufacturing Industry

Dr. Muhammad Nauman (Pharm-D)[1], Rehana Bano[2]
1(Hamdard Institute of Education and Social Sciences)
2(Getz Pharma Private Limited)

Abstract : *The purpose of Quality Risk Management is to illustrate practical ways to analyze the risks to quality system, providing guidance along the way to achieving effective and efficient quality management and compliance. In the pharmaceutical manufacturing every product and every process associated with risks. To maintain product quality throughout the product life cycle, too much time and resources are allocated. Risk is described in -recent guidance as a combination of the probability of occurrence of harm and the severity of that harm. The Quality Risk Management (QRM) approach initiated by regulatory agencies with recognized management tools along with support of statistical tools in combination allows for a risk-based approach to quality management, thus ensuring that resources are deployed in a timely and expeditious manner to areas that need them most and proactive approach to compliance of good manufacturing practices (GMP).*

Keywords : *FMEA , HACCP ICH Pharmaceutical Industry, Quality Risk Management, Risk Assessment, Risk Control, Risk Identification, WHO. Gezt Pharma*

I. INTRODUCTION

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of quality risk management in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. However, achieving a shared understanding of the application of risk management among diverse stakeholders is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/ or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate Quality Risk Management

industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

Principles Of Quality Risk Management:

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.

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools.

- 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.

II. SCOPE

This Project will be used to address known issues or to implement continuous quality improvements. These requirements apply to all GMP operation and areas new and existing process method, utilities, equipment, and procedure. This describes the framework and principles for a science-based risk management system for cGMP It will provide basis of tools for quality risk management that can be applied to different aspects of pharmaceutical quality system. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug products (including the use of raw materials, solvents, excipient, packaging and labeling materials in drug products

III. DESCRIPTION AND METHODOLOGY

Objective of the Quality Risk Management For any pharmaceutical organization, Quality Risk Management should aim at raising the level of protection for the patient, by the reduction of the risk to which that patient is exposed at the time he receives a drug product.

This general objective can only be achieved if the implemented policy of Quality Risk Management exceeds the unique intend of GMP compliance by increasing the control of the Organization on developed (or under development) processes to improve:

- Relevance of implemented processes;
- Knowledge within the Organization;
- Confidence in performed operations. At the opposite, Quality Risk Management should not set for finality:
- Adjustment of controls to the currently available resources in the Organization;
- Provision of a wrongfully validated excuse not to comply with the regulatory requirements.

General Approach towards the implementation of Quality risk management system is described as under

3.1 Initiating the risk Management process:

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- Identify a leader and necessary resources;
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

Following are the steps that are furnished for the execution of risk management, (Fig. 01)

All area responsible persons identified the critical steps involve in drug process, equipment with their most significant risk and assign individual responsibility for managing the risk. Risk management will be initiated when it is intimated by the area responsible to QA for review / approval and implementation for new product/

change in product process or formulation / change in critical process parameter or change in any other system directly impacting the quality of product. This may include the following but not limited to.

- Deviation/Non-conformance-Procedure
- Product complaints-Procedure for handling products complaints
- External and internal audit observation
- Root cause analysis(Cause and effect analysis)
- Product quality reviews
- Any issue that require mid-term and long-term corrective and preventive action, with formal tracking and documentation
- Recommendation and executed validation
- Any Accident and Incident
- Out of specification result (OOS)
- Change Management
- Recalled
- Stability result failure
- Reliability of electronic data
- Numbering and significance of Quality defect(e.g: Recall etc)

To define the frequency and scope of audits, both internal and external, taking into account factors such as:

- Existing legal requirements;
- Overall compliance status and history of the company or facility;
- Robustness of a company's quality risk management activities;
- Complexity of the site;
- Complexity of the manufacturing process;
- Results of previous audits/inspections;
- Major changes of building, equipment, processes, key personnel;
- Experience with manufacturing of a product (e.g., frequency, volume, number of batches);

Test results of official control laboratories

3.2 Risk Assessment:

Risk assessment consists of Identification of hazards and the analysis and evaluation of risk associated with exposure to those hazards. The steps include risk identification, risk analysis and risk evaluation. It began with the general question, what are the principal factors important in predicting adverse impacts to drug quality?" Specific questions considered, directly or indirectly, in identifying candidate risk factors included:

- What hazards (sources of harm) related to manufacturing can adversely impact drug quality attributes?
- What variables are associated with, or predictive of, those hazards?
- What processes and process parameters are critical for quality attributes?
- What factors may affect the identified hazards and critical parameters and processes?
- What factors are predictive of high or low quality manufacturing?

Use below mentioned risk scales, as appropriate, to evaluate risks not already addressed through a gap assessment process. The factor uses to evaluate the risk are Severity, Likelihood and Detection

3.3 Severity:

The severity of the negative impact that will accompany an adverse event. This is expressed on scale deemed appropriate (High to Low). Table-01

3.4 Likelihood/Probability:

The likelihood of an adverse event occurring this is measured on a relative scale such as across a time period or number of operations (Probable to improbable). Table-02

3.5 Detection:

The likelihood that a negative condition will be detected before the negative impact occurs.

- Determine the severity of the risk based on the descriptions provided in Table 1.
- Determine the Likelihood of the risk based on the descriptions provided in Table 2.
- Determine the Detection that will mitigate the risk based on the descriptions provided in Table 3.
- Calculate the risk level by multiplying the severity by the Likelihood by the Detection. Locate the risk level in Table 4.

- Locate the expected activities in table 4 (SxLxD Risk Level). Table-03 & 04

3.6 Risk Analysis

The risk level is based on the assign severity, the probability of Likelihood and the ability to detect failure mode or prevent the failure cause, a quantitative number (SxLxD) that is called Risk priority number (RPN), as well as resulting quantitative risk level
[H= High,
M= Medium,
L= Low is provided in the below:
*S (Severity), L (Likelihood) and D (Detection)

3.7 Risk Evaluation

This table displays the risk classification method used in the assessment process. It is the compression of the estimated risk to given risk criteria using a quantitative and qualitative scale to determine the significance of the risk. (Table-05)
SxL: A risk level threshold is established base on the severity rating multiplied by the Likelihood rating.
Risk assessment Report will be complied by owner and approved from head of QA

3.8 Selection of Risk Management Tool

Below mentioned tools are adapted to address the risk for specific area pertaining to the nature of risk.

- HACCP (Hazard Analysis Critical Control Point)
- FMEA (Failure Mode Effect Analysis)

3.9 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

3.10 Risk reduction

Risk owner will prepare the mitigation plan for each individual risk. The mitigation plan will cover all the risk according to the priority level. Risk will be analyzed and the probable root causes will be identified to determine the future corrective and preventive actions.

Note: If required risk team will be formed depending upon the nature of the risk otherwise risk owner can work himself monitor the progress of risk commencement to end.

3.11 Risk acceptance

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.

3.12 Risk review

QA reviewed the progress of the risk management process to consider new knowledge and experience, it is an ongoing quality management process. Review issues in the quality systems, manufacturing, etc., that could impact the product safety and efficacy or product availability. e.g., CAPA, Complaint, Validation, lot manufacturer, stability, testing and existing system (Inspection audit, change control).The risk review team will review quarterly or as required the status of all risk mitigation plans depending upon the level of risk. The outcome of the risk review will be documented and the risk register will be updated to reflect actions and decisions taken. Risk management is a part of an integrated Quality Management System that includes documentation (To review current interpretation and application expectations and to determine the need and/or develop the content for SOPs, guidline.etc.)Training, Quality defects, Audit/Inspection, Periodic review and Change management/Change control ((Evaluate the impact of the changes on the availability of the final product. Evaluate the impact on product quality of changes to the facility, equipment, material,

manufacturing process or technical transfers To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators).

IV. FIGURES AND TABLES

Figure: 01

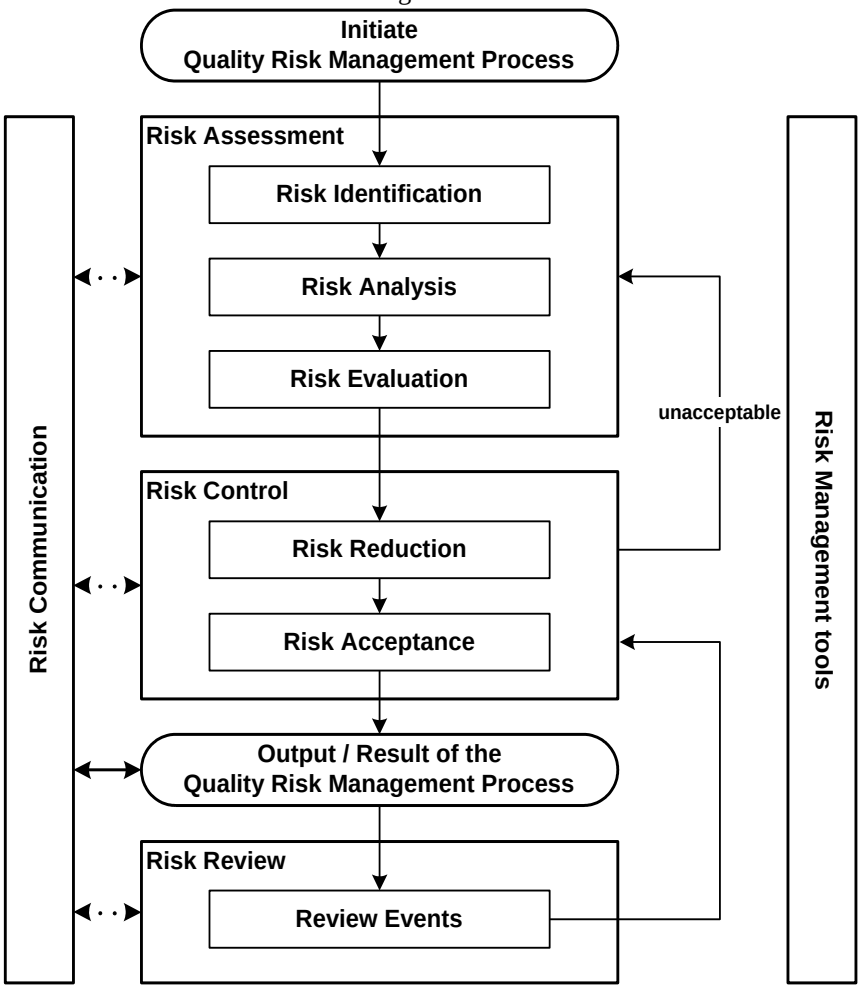

Table 01: Severity

Severity Rating	Description
4	• Product functionality in affected: • Failure to meet specifications related to patient safety and efficacy resulting in. • Batch that could not be reworked causing an investigation, potential stock out • Compliance issue resulting in Plant shutdown; • Significant Regulatory impact (e.g. warning letter, failure to gain approval to ship product from the site). • Medical: The failure mode effect could result in death or life threatening injury
3	• Product quality is affected, and the failure mode effect could result in failure to meet specifications related to Quality Attributes • Minor defects detected during inspection • Batch re-process with man-hour impact; resulting investigation • Possible regulatory impact; regulatory inspection observations without significant impact on the plant
2	• Product quality is affected, but the failure mode effect results in cosmetic defects Attributes. • Cosmetic defects noted during inspection: risk is considered acceptable. • Possible impact on yield, manufacturing efficiency • Deviation; can be closed without further Investigation
1	• Risk is considered acceptable. Product functionality and quality is intact. • Medical: Product functionality is intact. No safety impact. Minor alterations in the product result in possible patient inconvenience.

Table 02: Likelihood

Likelihood Rating	Description
5	Probable: It has Likelihood and /or is likely to Likelihood regularly or *many times* during the life of the product under specified operating conditions.
4	Occasional: It has Likelihood and / or is likely to Likelihood *several times* during the life of the product under specified operating conditions
3	Possible: It has Likelihood and /or is likely to Likelihood *infrequently* during the life of the product under specified operating conditions
2	Rare: It has Likelihood *once*, and / or will rarely Likelihood or is very unlikely to Likelihood during the life of the product under specified condition.
1	Improbable: Failure impact is not expected to occur under specified operating conditions.

Table 03: Risk Matrix

Severity Scale	Likelihood/Probability of occurrence				
	Improbable(1)	Rare(2)	Possible(3)	Occasional(4)	Probable(5)
High(4)	Medium (4)	Medium (8)	High (12)	High (16)	High (20)
Medium(3)	Low (3)	Medium (6)	Medium (9)	High (12)	High (15)
Low to Medium(2)	Low (2)	Medium (4)	Medium (6)	Medium (8)	High (10)
Low(1)	Low (1)	Low (2)	Low (3)	Medium (4)	Medium (5)

Table 04: Detection

Result Rating	Description
1	High probability: 100% confidence, control will almost certainly prevent a failure cause or detect a failure mode.
2	Moderate probability: Controls may detect a failure cause or a failure mode
3	Low Probability: Controls may detect a failure cause or a failure mode.
4	Very Low Probability: Controls probability will not prevent a failure cause or detect a failure mode
5	No Controls: The failure is not detectable or is not routinely checked

Table 05: SxL Evaluation

SxL*	RPN#	Risk Level	SxL Evaluation
10-20	60-100	High	Assess current controls affectivity Evaluate the need for further action, such as new design (to lower severity) or new prevention control (to lower occurrence).
4-9	41-59	Medium	Risk/benefit analysis must clearly explain how the benefit of this product outweighs any patient residual risk.
1-3	>40	Low	Risk is considered acceptable and no need to consider further evaluation.

V. CONCLUSION

Based on the reviewed guidelines for the implementation of Quality Risk Management in pharmaceutical industry it is reveals that It can be applied to different aspect of pharmaceutical quality including development, Manufacturing, Distribution, Inspection, submission and review processes through the life cycle of drug substances and drug product. a

Illustrated overall risk guidance, modules, strategies, techniques and tools lead to the following conclusive points to pharmaceutical industry

QRM improves risk awareness and accelerates detection of potential issues by analyzing and comparing existing data from a quality perspective to manage product quality, manufacturing processes and compliance within a risk based Quality Management System.

QMR improves decision making if a quality problem arises, provides systemic processes designated to co-ordinate, facilitate and improve science-based decision-making with respect to risk.

Risk management can be performed with recognized management tools along with support of statistical tools in combination, which make easy for application of quality risk management principles.

Risk Management identifies hazards associated with a product, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the control.
An effective quality risk management ensures the high quality of drug product to the patient
Following are the most effective tools which can be used in pharma industries with variety of different application

- HACCP (Hazard Analysis Critical Control Point)
- FMEA (Failure Mode Effect Analysis)

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"Knowledge is like a fruit. When a fruit grows on a branch of a tree, its weight causes that branch to bend and bow. Similarly, when knowledge increases in a person, it causes him to become humble and not proud and boastful."

(Anonymous)

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REFERENCES

[1] http://www.ich.org/products/guidelines/quality/article/qualityguidelines.html
[2] http://www.ich.org/products/guidelines/quality/q9-briefing-pack.html
[3] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Q9_Briefing_Pack/Tools_-_Applications.pdf
[4] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf
[5] http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex7.pdf
[6] http://www.ibec.ie/Sectors/IMDA/IMDA.nsf/vPages/News_and_publications~Publications_and_Resources~qa-ra-forum-31-10-2012/$file/ChriisieKeaneDTR24971.pdf