International Journal of Research in Pharmacy and Science

Review Article

Opportunities and challenges in the implementation of ICH Q9 with emphasis to a WHO approved pharmaceutical plant

Venkatesh M.P., Nagendra S.R., Pramod Kumar T.M.

Regulatory Affairs Group, Department of Pharmaceutics, JSS College of Pharmacy, JSS University, SS Nagara, Mysuru, Karnataka

Address for Correspondence:
Dr. M.P. Venkatesh
Email: venkateshmpv@jssuni.edu.in

Access this article online	
QR Code	Website: www.ijrpsonline.com

ABSTRACT

Quality Risk Management (QRM) is one of the most important tasks when it comes to pharmaceutical industry, as the quality of products produced by it is directly related to patient health. International Council on Harmonization (ICH) has developed various guidelines to protect the quality of medicines manufactured by a pharmaceutical plant; one such is the ICH Q9 guideline. Implementing QRM is currently approaching to be a mandatory practice. But the question arises whether the guideline interpretation goes hand in hand with its implementation in the industries? There are still many things which need improvisation in aspects of interpretation and implementation of the harmonized guideline. ICH Q9 provides a standard path for the industries to practice risk management activities which allows a formal acceptance by GMP regulators. Industries and regulators can make use of various risk management plan such as European risk management strategy, risk management guidance, risk-ranking and filtering tool of 2004 of FDA. This article discusses the process of risk management to achieve quality of medicinal products and tools which can be used for risk assessment during manufacturing practices undertaken by small or medium sized WHO approved plants. Effective QRM implementation can facilitate better and well-versed decisions which can provide regulators with greater assurance of a company's ability to deal with possible risks. Considering the higher incidences of product recalls, the implementation of Q9 together with Q8 will help the Indian pharmaceutical companies to launch safer products in the market, which in turn benefits the industry and the patient.

Key words: *ICH Q9; Quality Risk Management; Risk- based approach; Patient safety; Product quality*

INTRODUCTION

Since a couple of years Quality Risk Management (QRM) has become a mandatory regulatory requirement towards healthcare organizations. QRM is an overall and continuing process of minimizing risks to product quality throughout its life-cycle in order to optimize its benefit and balance the risk. It is a systematic process for the evaluation, control, communication and review of risks to the quality of the medicinal product. It supports science based and practical decisions when integrated into quality systems, examples of quality systems include Validation, Quality Defects - Investigation, Auditing, Inspection, Documentation, Training etc.[1]

One of the most important requirements of the pharmaceutical industry is compliance with GMP. Pharmaceutical companies cannot market their drugs without it in the developed countries. There is a need to understand the process of QRM in management and the tools used as an approach to the implementation of it.

Quality Risk Management principles are effectively utilized in many areas including business, insurance, work related safety, public health, pharmacovigilance, and by agencies regulating these industries. Even though 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 relation to

pharmaceuticals, though there are a variety of stakeholders, including medical practitioners and patients as well as government and industry, the safety of the patient by managing the risk to quality should be considered prime importance.[2]

The manufacturing and use of a drug product, including its components, necessarily involve some degree of risk. An effective QRM approach can further ensure the high quality of the drug product to the patient by identify and control potential quality issues during development and manufacturing. Use of QRM can improve the decision making if a quality problem arises. Effective QRM implementation can facilitate better and well versed decisions which can provide regulators with greater assurance of a company's ability to deal with possible risks.

Updating the pharmaceutical plants and equipment has become a necessity with the passage of time. Present manufacturing techniques used in pharmaceutical industry lag far behind that used in a detergent industry or potato-chip industry. One cannot agree that quality of medicines can be similar to that of detergents. The US Food and Drug Administration (FDA) put this problem in a 2004 report as "Pharmaceutical manufacturing operations are inefficient and costly compared to other industrial sectors". The rate of introduction of modern engineering process design principles, new measurement and control technologies, and knowledge management systems is slow in the pharmaceutical industry. Risk is a mixture of possibility of occurrence of harm and severity of that harm as stated in ICH Q9 guideline. QRM mends decision making through systemic process chosen to co-ordinate, implement and improve science based approach. Since 2004, many pharmaceutical industries have started to use new technologies for their production and quality control areas. ICH Q9 provides a standard path for the industries to practice risk management activities which indicates a formal acceptance by GMP regulators of risk-based approach. Not only the industries follow it but even the regulators apply its concepts in their own work activities.[3]

There are various tools and programs such as FDA's risk ranking and filtering tool of 2004, EU Inspector's working party initiative of 2008 and PIC/S (The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme) and Risk based Inspection planning tool of 2011, developed by different regulatory bodies to suit their requirements. Prior to the use of risk management plan in an organization, establishment of a guidance document to help guide the risk assessment process is recommended. The guide can contain the categorization of risk parameters i.e. severity, probability and detectability for each element in the life cycle of a product.[4]

A few questions arising out of Q9 practice are:

1) Is risk analysis being used to prioritize critical-to-quality activities?
2) Is it used to continuously improve manufacturing process?
3) Is there a risk management process in place integrated into quality system?

OBJECTIVES

The objectives of this study are:

- To familiarize ourselves with the ICH Q9 guideline perspective of Quality Risk Management
- To get acquainted with the industry perspective of QRM
- To study the risk assessment tools of QRM

DISCUSSION

ICH Q9 - *Quality Risk Management* provides an excellent high-level framework for the use of risk management in pharmaceutical product development and manufacturing quality decision making applications. It is a landmark document in acknowledging risk management as a standard and acceptable quality system practice to facilitate good decision-making with regard to risk identification, resource prioritization, and risk mitigation / elimination, as appropriate.[5]

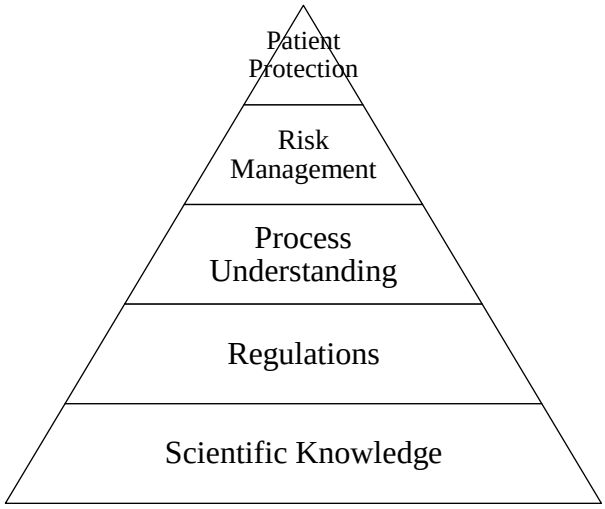

Figure 1: Quality Risk Pyramid

1) ***Principles of Quality Risk Management***

Two primary principles of quality risk management are:[6]

- 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.

2) ***General 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 (medicinal) product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1). Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.[7, 8]

Table 1: Risk Management *Case Study Assessment Criteria*[9]

***To be assessed for each case study*:**
1. Case study can be tied to one or more core GMP Systems.

2. Case study addresses a recognized area of general industry interest / application.
3. Case study uses an approach that is consistent with ICH Q9 concepts and direction.
4. Case study utilizes recognized quality risk management tools.
5. Case study is appropriately simple and succinct to assure clear understanding.
6. Case study provides areas for decreased and increased response actions.

***To access case study choices in aggregate*:**

7. Case study avoids excessive redundancy in subject and tools as compared to other planned models.
8. Case study balances use of quantitative and semi-quantitative tools.

3) *Risk Assessment Supporting Tools*

A key early step in the execution of a risk analysis is to determine the appropriate risk assessment tool (or methodology). There is generally no single best choice for any given assessment process, and the selection of the appropriate risk methodology should be based on the depth of analysis required, complexity of the subject risk of concern, and the familiarity with the assessment tool. Based on the industry examples reviewed by the Working Group

Risk Ranking & Filtering (sometimes referred to as *Risk Matrix*) and *Flowcharting* were the most popular tools used for basic risk assessment activities. Correspondingly, *Failure Mode Effect Analysis* appeared to be the most frequently used methodology for more advanced risk analysis efforts. Some examples demonstrated the power of combining tools to help in more complex analysis. For example, Fault Tree Analysis (FTA) or a Fish-bone diagram can be used to initially scope and evaluate the fault modes of a particular problem and then be used to feed a Hazards Analysis and Critical Control Point (HACCP) or similar tool to evaluate overall system control and effectiveness.[10, 11]

A list of generally well-recognized risk management tools is provided in Table 2: *Common Risk Management Tools*, to facilitate the reader's evaluation of potential alternatives. While the list is not inclusive of all available risk assessment methodologies, it represents some of the more frequently used approaches.

Each risk subject and assessment warrants consideration of the applicable descriptors of potential risk and related consequences. Ideally, firms should establish a guidance document ahead of any risk analysis, such as the one provided in Table 3: *Severity Categorization Table*, to help guide the risk assessment process and guide consistency in decision-making companywide.

QRM Process: In industries, QRM follows the most common fashion of management practices like forming a multidisciplinary team in the beginning. The team then at first defines a risk question which will help link to the patient safety i.e. any actions taken as a part of QRM should not affect patient health in a negative way. The risk question also helps to understand which assessment tool is to be selected and the process at once. Then the actual analysis and evaluation of the risks associated with a process or product is started with the help of a single tool or combination of tools. Usually it is believed in industry implementation that no single standardized tool helps in complete assessment of risks present in the organization. Hence a combination of variety of tools (formal or informal) is suggestive of use.

The risk assessment process involves three steps. First step is the risk identification, where a list of potential risks involved in the target process or a complaint is listed, followed by risk analysis, where the potential harms of the risks are calculated either qualitatively or quantitatively or in both ways for better analysis and decision making. The third step forms the decision making step where it is decided that which risks are to be reduced and which are acceptable; it is important that any decision is indeed to be justified.

Following the risk assessment, a review of risks is done to analyze whether the action taken brought a positive output or not (i.e. whether the target is achieved; the target can be for instance, reduction of risks present to 50%). All these steps are finally communicated to the stake holders involved with the company, particularly the QRM and documented. It is said, "*If it is not documented, it is not done*". The QRM process is briefly outlined in Fig. 2.[13]

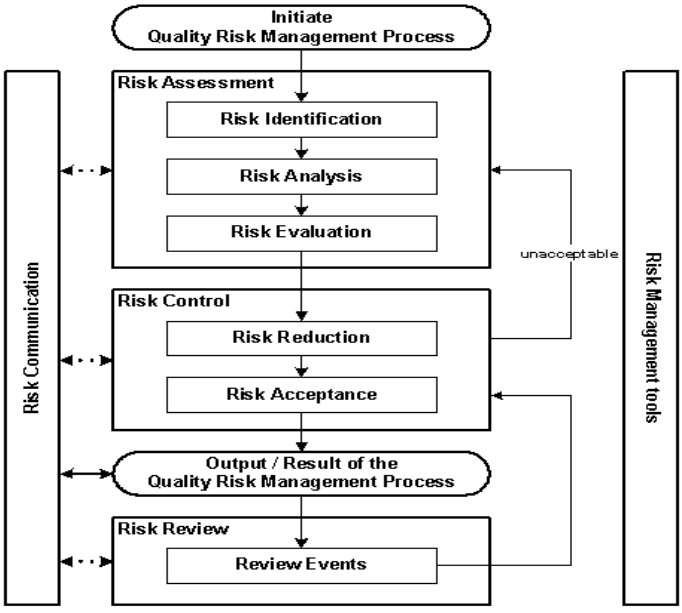

Figure 2: ICH QRM Process

Table 2: Common Risk Management Tools[12]

Risk Management Tool[a]	Description / Attributes	Potential Applications[b]
Basic Tools		
Diagram Analysis • Flowcharts	▪ Simple techniques that are commonly used to gather/organize data, structure risk	✓ Compilation of observations, trends, or other empirical information to support a

• Check Sheets • Process Mapping • Cause/Effect Diagrams	management processes, and facilitate decision making.	variety of less complex deviations, complaints, defects, or other circumstances.
Risk Ranking and Filtering	▪ Method to compare and rank risks ▪ Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk scores.	✓ Prioritize operating areas / sites for audit/assessment. ✓ Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool.
Advanced Tools		
Fault Tree Analysis (FTA)	▪ Method used to identify all root causes of an assumed failure or problem. ▪ Used to evaluate system/sub-system failures one at a time, but can combine multiple causes of failure by identifying causal chains. ▪ Relies heavily on full process understanding to identify causal factors	✓ Investigate product complaints ✓ Evaluate deviations
Hazard Operability Analysis (HAZOP)	▪ Tool assumes that risk events are caused by deviations from the design and operating intentions ▪ Uses a systematic technique to help identify potential deviations from normal use or design intentions.	✓ Access manufacturing processes, facilities, and equipment ✓ Commonly used to evaluate process safety hazards.
Hazards Analysis and Critical Control Points (HACCP)	▪ Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring ▪ Bottom-up approach that considers how to prevent hazards from occurring and/or propagating ▪ Emphasizes strength of preventive ▪ controls rather than ability to detect ▪ Assumes comprehensive understanding of the process and that critical process parameters (CPPs) have been defined prior to initiating the assessment. Tool ensures that critical process parameters will be met.	✓ Better for preventive applications rather than reactive ✓ Great precursor or complement to process validation ✓ Assessment of the efficacy of CPPs and the ability to consistently execute them for any process
Failure Mode Effects Analysis (FMEA)	▪ Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance. ▪ Once failure modes are known, risk reduction actions can be applied to eliminate, reduce, or control potential failures. ▪ Highly dependent upon strong understanding of product, process and/or facility under evaluation. ▪ Output is a relative "risk score" for each failure mode.	✓ Evaluate equipment and facilities; analyze a manufacturing process to identify high risk steps/critical parameters.

[a] Sample list of key risk management tools – others (not listed here) may apply for a specific application
[b] Examples only

Implementation: For starters, the evaluation of any product/ process requires the right team for the work. The stakeholders included in QRM of a product/process constitute inter-multidisciplinary team with sufficient expertise of relevant operation. The stakeholders can be divided into categories; Responsible, Accountable, Consulted and Informed, shortly known as RACI. Responsibilities will be as per the criteria of division named above and is shown in Table 3. Following this, the team can define risk in question attributed to a target process/product.

The risk question should also be agreed upon as to linking the risk evaluation and any action with protection to patient. The risk identification as said forms the first step in the assessment process. There are various tools namely brainstorming, what if?, mind mapping, check-sheets, flowcharting, process mapping,

cause and effect analysis/fish bone diagram, hazard operability analysis (HAZOP), hazard analysis and critical control point (HACCP) etc., for risk identification.[14, 15]

Risks are associated with each and every step in a plant. Which risk is of potential harm and which can be resolved at a later stage should be known, and hence prioritization is of importance.

Table 3: "RACI" Interdisciplinary Team Roles and Responsibilities

Roles	Responsibilities
Responsible	Doers
Accountable	Approver/ final approver
Consulted	Those whose opinions are sought and with whom there is two way communication
Informed	Those who are kept up-to-date on progress, usually on completion of the task or at key milestones. One way communication

Table 4: Severity Categorization Table[18]

Severity of Consequences	Category			
	Patient Safety	**Regulatory Compliance**	**Product Supply**	**Other**
5 - Catastrophic	Use of product will cause a serious health consequence. Patient safety is affected by product safety that is either a function of product design or a manufacturing defect.	Consent decree, product seizure, regulatory imposed cessation of operations or equivalent.	Market stock out (patient impact) of medically significant products.	Subject specific issues may warrant the consideration of other regulatory or business impacts e.g.: 1. company reputation 2. "current" GMP practices within industry 3. evolving regulation Differentiation around the severity of consequences may also need to include these or other areas of interest / potential impact as well.
4 - Very Serious	Use of product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. Degree of seriousness is subject specific.	Major observations or regulatory warning letter. Practices/facility not aligned with regulatory requirements, and there is no technical justification for approach. GMP license in jeopardy of being suspended or withheld.	Market stock out (patient impact) of non-medically significant products.	
3 – Serious		Repeated and/or multiple minor observations. Practices and/or facility not aligned with current GMP expectations, but there is technical justification for the site's approach.		
2 – Important	Highly unlikely that use of product will cause an adverse health consequence.	Few minor observations / comments. System gaps.	Product back-orders (no patient impact) resulting in active efforts to allocate supply to avoid patient impact.	
1- Noticeable	No probability of patient impact.	One-off audit findings. Minor system gaps.	Product backorders (no patient impact) resulting in temporary shortage to wholesalers.	

4) ***QRM Tools***

Risk Identification tools: Selected examples of risk identification tools are flowcharting and fishbone diagrams. Flowcharting is the process of charting a process or information by representing the individual steps as boxes and displaying the order of occurrence by connecting each box with an arrow showing the direction of process / information flow. It is through process understanding that flowcharts can be used to aid risk Identification in identifying potential issues, hazards, defects, bottlenecks and restrictions. Flowcharting of processes in more detail is commonly known as process mapping. Fishbone Diagrams (also known as cause and effect diagrams or Ishikawa diagrams) are also used to identify causes associated with an event, but are easily adopted to identify hazards / risks associated with an event. The head represents the problem or

risk in question, the spine of the fish with branches coming from it representing the causes and the sub-branches the reasons. Often the more populated the bone is the more influential that category is to overall risk. Risk analysis and evaluation tool: Major risk analysis tools are "**Risk ranking and filtering tool**" and "**Faulty Mode Effect Analysis (FMEA) tool**". Risk Ranking is a method used to compare risks and it typically involves both qualitative and quantitative approach to analyze each identified risk (qualitative factor – e.g.: Weighting factors, quantitative factor – e.g.: Risk Score). This in its simplest form leads to a two-dimensional diagram of probability of occurrence measured against the severity of the consequences if it occurred. The technique works by breaking down the two measures used i.e. probability of occurrence and the severity of the outcome into verbal scales to give a two dimensional view. The weighting for severity and frequency can be modified as per the risks of a particular organization depending on the application and focus required.[16,17]

Every organization's initial goal towards implementation of quality risk management is to maintain a guide of important risk parameters. It depends on the team to select a ranking and the parameters for analysis for the target product/process. Table 5 shows the risk ranking score with three point scale and the risk evaluation scoring is shown in Table 6.

Table 5: Risk Ranking Scale – Process Deviation[19]

Numerical ranking	Severity	Frequency of Occurrences	Detectability	Max Risk Score
1	Potential minor patient injury but not permanent. Minor Regulatory compliance issue that can be corrected.	Isolated	High ability to identify the risk and take action to avoid	1
2	Potential serious injury, but not permanent. Significant regulatory compliance Issue	Moderate	Moderate	8
3	Potential death or permanent injury, Major regulatory compliance issue	Inevitable	Low ability to detect	27

Table 6: Risk Evaluation Score – Process Deviation[20]

Hazard	Risk Reduction controls	Frequency	Severity	Detection	Risk Score
Patient may receive empty capsules	A medical opinion was requested: Given the anti-epileptic indication, there is the risk of status epileptic us, which may be life threatening; since the capsules are opaque, patients will be unaware of the potential problem	2	3	3	18
Patient may not have medically needed product available	Incident impacted only single lot, so supply is not significantly impacted	1	1	1	1
Could receive an audit either internally/ regulatory agency	Comply with requirements of deviation investigation and notification to management, Field Alert Issued to FDA; complaint and Deviation GMP requirements met via compliance to SOPs	2	2	2	8

The company targets a score greater than the moderate score for risk evaluation and control. As per the table, the moderate score is 8, above which risk needs to be controlled to the accepted level, below which the risk is accepted and if any risk cannot be lowered below moderate score, the risk will be considered unaccepted.

Defining Risk Matrix: This allows graphical display of the total of each of the harms that contribute to risk. It is done by taking "severity" on X-axis and "probability" on Y-axis, the multiplication of these two measures gives the risk score which assists in prioritizing i.e. which risks to be controlled first and which ones later. First thing is to pick the categories involved in the risk matrix and breakdown them into scales and it is specific for an organization. The organization can then break risks into three regions 1) "Generally acceptable" (GA) region with low severity and probability, 2) "As Low As Reasonably Practicable" (ALARP), the middle region between the broadly acceptable region and the intolerable region, 3) "Generally unacceptable" (GU) region with high severity and probability (something bad is going to happen).[21]

Risk Documentation and communication: Each and every step of risk management program and most importantly the output is to be documented and made available. Site procedures also require approval of the deviation report. The risk analysis and the decision of product recall can be discussed in the internal management meetings and the discussions in the minutes can result in conclusive decisions. Most importantly, the regulatory agencies concerned are formally notified of the product recall.

Risk review: The product received from the product recall can be further examined as a part of risk review. An evaluation of the product complaints received and the adverse events reported

during the empty capsule use, can give a better understanding of the effect of such cases.

5) ***Risk Management Methodology***

Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk.[22, 23]

Informal ways (empirical and/ or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.

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.

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g., Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/ or criticality of the issue to be addressed.

6) ***Integration of Quality Risk Management into Industry and Regulatory Operations***

Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems. As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, 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 might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.[24]

Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes. Quality risk management should be integrated into existing operations and documented appropriately.

While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

CONCLUSION

The real benefit of applying QRM in medicines manufacturing has yet not been realized. It plays an important role in terms of:

- Safer medicines for patients
- More cost effective and efficient approaches to qualification, validation, change control and other quality control areas.
- Opportunities to achieve regulatory flexibility to some extent

Much effort has been put into for improving the quality of medicinal products and is now being incorporated in the regulatory framework. Still there are a lot of issues in this area which need attention. QRM helps in managing the risks to patients and for the company. Various manufacturing problems still arise at a later period or during batch release, resulting in complicated and costly investigations and other serious quality defects and ultimately results in product recall and in cessation of a batch. The real benefit of applying QRM in medicine manufacturing is to obtain safer medicines for patients. It also allows cost effective and efficient approaches to qualification, validation, change control and other quality control areas. By adopting the ICH Q8, Q9 and Q10 into the quality system of a company can ensure safety and thereby profit for our pharmaceutical companies in the long run:[25]

1. There would be better regulatory compliances
2. There would be fewer product complaints and recalls
3. There shall be an overall increase in customer satisfaction
4. There shall be a cumulative growth in business and market share.

REFERENCES

1. Guidance for industry "Q9 Quality Risk Management" by US department of Health and Human Services, Food and drug Administration, Center for Drug and Evaluation Research, [online] 2006. [Cited 2017 January 16] Available from: URL: https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf
2. Implementation of ICH Q9 in the pharmaceutical field an example of methodology from PIC/S [online] 2010. [Cited 2017 January 18] Available from: www.ich.org/products/guidelines/quality/quality/quality-risk-management.html
3. Risk Management of GMP Audits in Australia. Webinar. Tony Gould. [online] 2017 [Cited 2017 January 20] Available from: URL: http://apps.who.int/medicines/areas/

quality_safety/regulation_legislation/icdra/2_Australia_RiskManagement-GMPInspections.pdf
4. Risk Management Programs for the Pharmaceutical Industry by Edward Griffith. [online] 2017 [Cited 2017 January 23] Available from: URL: http://www.fujitsu.com/downloads/SVC/fc/wp/pharma-risk-mgmt.pdf
5. Risk Management for pharmaceutical industry. USFDA. March 2004. Solutions. [online] 2014 [Cited 2017January 25] Available from: URL: www.Pharmpro.com/riskmanagementforpharmaceuticalindustry
6. WHO Guideline on Quality Risk Management A draft guidance August 2010. [online] 2010 [Cited 2017 January 27] Available from: URL: http://www.who.int/medicines/services/expertcommittees/pharmprep/QualityRiskManagement-QAS10-376_18082010.pdf.
7. Ranjana Suryawanshi, Aparark Mohalkar, Radhabai Jadhav, Manjusha Bhange, Ashwini Jankar. Implementation of Quality Risk Management (QRM) in Pharmaceutical Industry: A Review. World Journal of Pharmaceutical Research 2015; 4(11):724-733.
8. Risk assessment and quality control by Max Williams, MPA. [online] 2012. [Cited 2014 February 1] Available from: URL: http://sphinxsai.com/2014/phvolpt3/1/(908-914).pdf
9. Quality Risk Management Principles and Industry Case Studies by T. Frank. [online] 2014 [Cited 2017 February 3] Available from: URL: www.pharmtech.com/quality-risk-management-principles-and-pqri-case-studies
10. A Guide to Supply Chain Risk Management for the Pharmaceutical and Medical Device Industries and their Suppliers. [online] 2016 [Cited 2017 February 6] Available from: URL: http://www.thecqi.org/Community/Special-Interest-Groups-SIGs/Pharmaceutical-Quality-Group/PQG-guide/
11. Frank T, Brooks. S, Creekmore. R, Hasselbach. B, Murray. K, Obeng. K, et al. Quality Risk Management Principles and Industry Case Studies. Product Quality Research Institute [online] 2008 [Cited on 8th February 2017]; Available from: URL: http://www.pqri.org/pdfs/MTC/Quality_Risk_Management_Principles_and_Industry_Case_Studies_December_28_2008.pdf
12. EtQ's Webinar [Internet]. Risk Management 2.0 The expanding role of Risk Mitigation in Industries. [online} 2011 [Cited 2017 February 10]. Available from: URL: http://online.wsj.com/news/articles/SB10625358403931000?mg=reno64-wsj&url=http%3A%2F%2Fonline.wsj.com%2Farticle%2FSB10625358403931000.html
13. Amrita Das, Praveen Kadwey, Jai Kumar Mishra, Sudheer Moorkoth. Quality Risk Management in Pharmaceutical Industry: Tools and Methodology. International Journal of Pharmaceutical Quality Assurance 2014; 5(3); 13-21.
14. V Vijayakumar Reddy, N Vishal Gupta, H V Raghunandan, U Nitin Kashyap. Quality Risk Management in Pharmaceutical Industry: A Review. International Journal of PharmTech Research. 2014; 6(3): 908-914.
15. Reham M. Haleem, Maissa Y. Salem, Faten A. Fatahallah, Laila E. Abdelfattah. Quality in Pharmaceutical Industry: A Literature review. Saudi Pharmaceutical Journal 2015; 23(5):463-469.
16. Quality Risk Management – The Pharmaceutical Experience by Ann O'Mahony. [online] 2009 [Cited 2017 February 20] Available from: URL: https://www.scribd.com/document/295806538/Quality-Risk-Management-the-Pharmaceutical-Experience
17. Technical Report No. 54-3 Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations. [online] 2009 [Cited 2017 February 22] Available from: URL: https://store.pda.org/TableOfContents/TR54-313_TOC.pdf
18. Guidance for Industry: Q9 Quality Risk Management. USFDA. [online] 2006 [Cited 2017 February 24] Available from: URL: https://www.fda.gov/downloads/Drugs/Guidances/UCM070337.pdf
19. PIC/S. Quality Risk Management – Implementation of ICH Q9 in the Pharmaceutical field an example of methodology from PIC/S. [online] 2006 [Cited 2017 February 27]. Available from: URL: http://www.picscheme.org/pdf/65_psinf012010exampleofqrmimplementation-copy1.pdf.
20. Irish Medicines Board. Improving Quality Risk Management Activities to better support GMP Activities. [online] 2010 [Cited 2017 March 1]; Available from: URL: http://www.imb.ie/images/uploaded/documents/GMP%20info%20day%20presentations/4.1%20Improving%20Quality%20Risk%20Management%20activities%20to%20better%20support%20GMP%20Activities.pdf.
21. Report Linker. Pharmaceutical Industry: Market Research Reports, Statistics and Analysis. [online] 2017 [Cited 2017 March 3]. Available from: URL: http://www.reportlinker.com/ci02257/Pharmaceutical.html
22. Risk Management: Guidelines and Best Practices Missouri Information Technology Advisory Board Project Management Committee Risk Management Subcommittee [online] 2003 [Cited 2017 March 6] Available from: URL: www.wjpr.net/download/article/1446280617.pdf
23. Risk Management - Vocabulary - Guidelines for Use in Standards, International organization for standardization [online] 2002 [Cited 2017 March 8] Available from: URL: https://www.theirm.org/media/886059/ARMS_2002_IRM.pdf
24. International Organization for Standardization. ISO 14971:2007 Medical devices – Application of risk management to medical devices. [online] 2002 [Cited 2017 March 10] Available from: URL: https://www.iso.org/standard/34998.html
25. ICH guideline: Quality Risk Management Q9. Current Step 4 version dated 9 November 2005. [online] 2005 [Cited 2017h March 13] Available from: URL: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf