

Quality Risk Management (QRM) in Pharmaceutical Industry: Tools and Methodology

Amrita Das¹, Praveen Kadwey¹, Jai Kumar Mishra², *Sudheer Moorkoth³

¹Department of Pharmaceutical Regulatory Affairs, Manipal College of Pharmaceutical Sciences, Manipal, 576104

²Regulatory Affairs in-charge, Tirupati Medicare Limited, Ponta Sahib, Himachal Pradesh, Sirmour, 173025, India.

³Department of Pharmaceutical Quality Assurance, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, 576104, India

Available Online: 1st July 2014

ABSTRACT

Quality risk management (QRM) is one of the most important tasks when it comes to pharmaceutical industry. It is because the industry produces medicines, whose quality is directly related to the patient health. International Conference on Harmonization (ICH) has developed various guidelines to protect the quality of medicines along with its safety and efficacy. QRM is currently approaching to be a mandatory practice in industries. ICH Q9 guideline can help industry start with its risk management plan but its implementation and practice seems to be challenging. There should be a risk management plan in place together with QBD (Quality by Design) and PQS (Pharmaceutical Quality Systems) to build quality in the final product. Being a non-mandatory requirement till now, industries hesitate to implement the new paradigm, Q8, Q9 and Q10, which will become a burden for industries to meet the regulatory challenges. But it is important to understand that it is high time to bring a change which is risk free. 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. 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: Quality risk management (QRM), ICH Q9, Implementation, Tools, Methods, Process, Technology transfer

INTRODUCTION

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⁽¹⁾. 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⁽²⁾. 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.

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⁽³⁾. 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. 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? The degree of implementation of these aspects globally is shown in Table 1. Top risks that keeps a company awake at night (focusing on the manufacturing operations) are product recalls, failure of a critical asset, non-compliance, supplier non-conformance, employee health and safety, environmental impact and time to launch the product to market. Potential applications of QRM are listed in the Table 2, and it covers the entire products life cycle. The

*Author for correspondence: E-mail: sudheermoorkoth@gmail.com

Table 1: Degree of implementation of QRM practice globally

Degree of Implementation	% (Global)	Ranking	% Ranking (EU)	% Ranking (Non-EU)
Critical to quality prioritization	65		64	67
Manufacturing process risk analysis	59		49	63
QRM integration in Quality System	63		56	73

Table 2: Potential applications of QRM

Potential applications of QRM	
Integrated Quality Management	Documentation, Training, Auditing, Periodic review, Change control
Regulatory Operations	Auditing planning & frequency, Evaluation of significance of potential recalls
Development	Establish a design space, Product & manufacturing process, Critical control parameters, Technology transfer
Facilities, equipment and utilities	Design of facility, Hygiene aspects, Cleaning of equipment- CIP, Calibration maintenance, Computer controls
Materials Management	Suppliers & contract manufacturers, Starting material, Use of materials, Storage, Logistics
Production	Validation, In-process sampling & testing, Production planning
Packaging & Labeling	Design of packages, Selection of container & closure systems, Label controls
Laboratory control & Stability studies	Out Of Specification, Retest period

specific objective of this article is to understand the standard QRM tools and training methods with a regulatory and industry perspective. A case study on Q9 implementation pertaining to manufacturing of medicinal products is also discussed.

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. 1.

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-multi disciplinary team with sufficient expertise of relevant operation. The stakeholders can be divided into categories; Responsible, Accountable, Consulted and Informed, shortly known as RACI⁽⁴⁾. 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^(4,5,6). The case

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: Examples Of Criteria Used To Assess Risk Measures

Risk Measures	Scale	Examples
Severity	Catastrophic - 5	Quality issue with potential impact to patient safety, Significant production problem (atypical event in production causing major loss to supply)
	Major - 4	Quality impact, Major non-compliance (miscounts, mislabels), Impacts production for long period (long equipment downtime, rework)
	Moderate – 3	Quality concerns (customer complaints), impact production for a short period of time
	Minor – 2	Small quality and production issues (scuff label, more rejects)
	Not noticeable - 1	No quality impact, insignificant production or financial impact
Probability	Frequent – 5	100 events per year
	Probable – 4	10 events per year
	Occasional - 3	1 event per year
	Remote – 2	1 event every 10 years
	Improbable - 1	1 event every 100 years
Detectability	Scale	
	5 – Detected by consumer	
	4 – Detected during Finished Product Testing	
	3 – Detected during subsequent unit operations	
	2 – Detected during a unit operation	
	1 – Detected before unit operation	

taken as an example in this paper does not use a particular tool for risk identification, as the risks are identified in a simple way. The flowcharting is used as an example to show the analysis of the target cause of the case (i.e., the process deviation resulting in empty capsules production in this case), as shown in Fig. 2. This can be said as a retrospective approach to risk analysis. Followed by the analysis of the resulting empty capsules, an inventory evaluation was performed, which showed that there were one to five empty capsules out of 46% of the bottles evaluated.

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. If observed, rather than resolving the equipment issue, it is more important to know whether the empty capsules released can impact the patient in any way and also the company. The risk question is; “Do a small number of potential low fill or empty capsules in a single batch of PainFree® capsules pose an unacceptable risk to patients, and secondarily, to the company?” The potential risk identified in this case is chances of receipt of empty

capsules by the patient and thus unavailability of medically needed product⁷.

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 illustration of it is shown in Fig. 3 wherein 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

Table 5: Risk Ranking Scale – Process Deviation

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

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 and/or 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

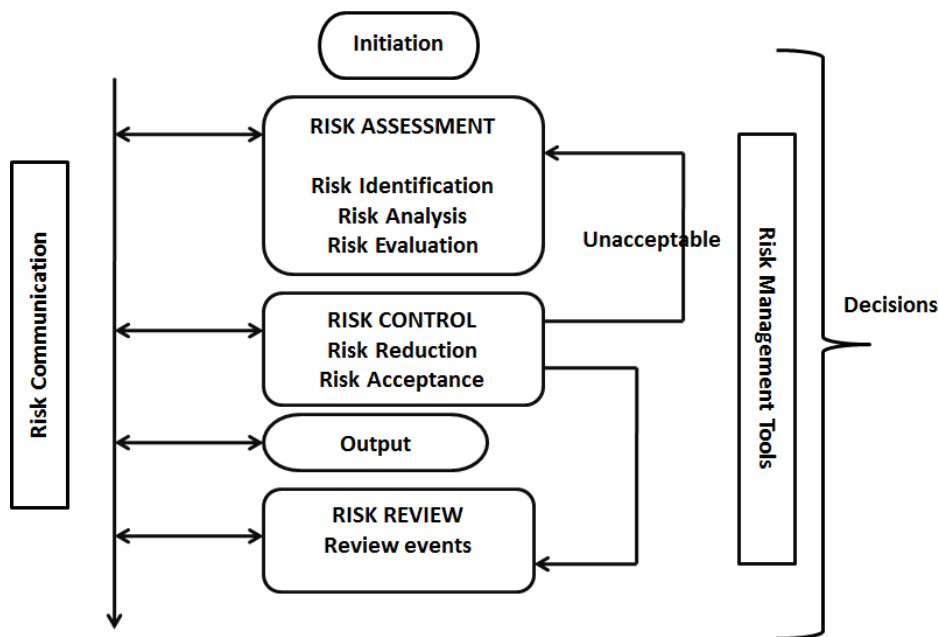


Fig. 1: The QRM process

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

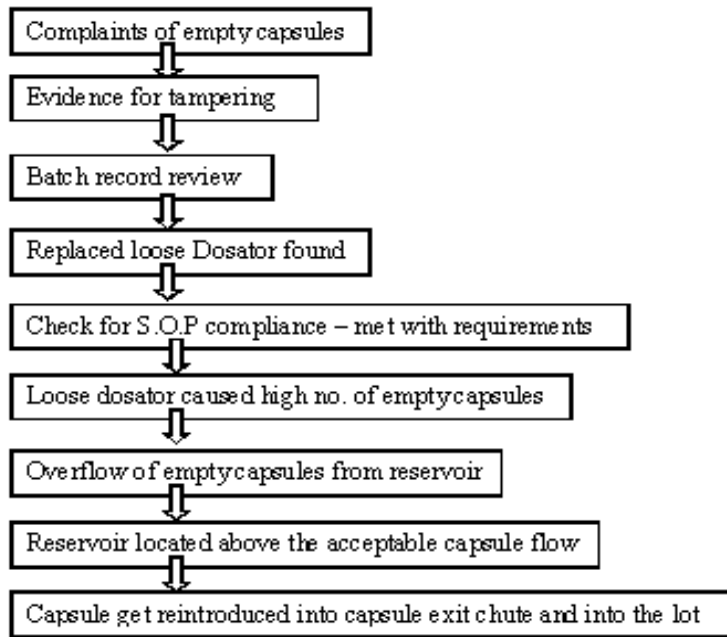


Fig. 2: Flowchart of Process Deviation – Empty Product Capsules

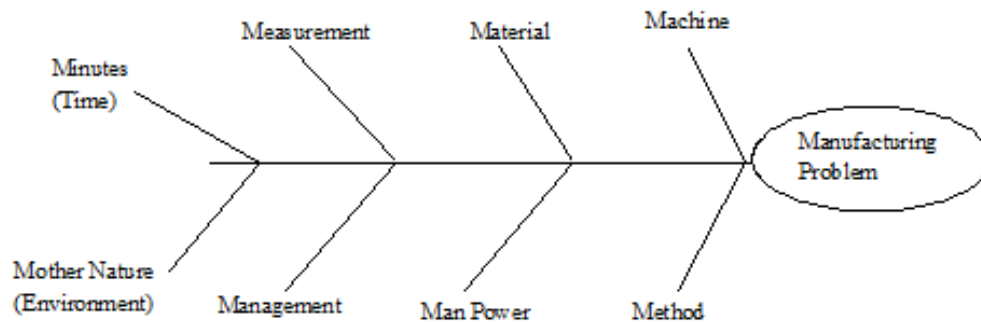


Fig. 3: Fish bone diagram

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 (example, shown in Table 4). The weighting for severity and frequency can be modified as per the risks of a particular organization depending on the application and focus required.

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.

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 unacceptable. Based on the evaluation, it is seen that though there were very less number of empty capsules or less filled capsules found during inventory check, there is no idea of the number of empty capsules actually released into the market, moreover the administration of such capsules by specific patient group results in severe consequences. As all the batches of the capsules were released and the incapability of the company to reduce the risk in terms of severity and detectability (as the capsules were opaque), there was nothing much to do except initiating product recall. This formed the part of risk control. Also, as a part of internal risk control i.e. to prevent risk due to the encapsulation equipment, an automated sensor was attached to the reservoir collecting empty/rejected capsules by means of which the encapsulation machine shuts down automatically when the sensor gets activated, thus preventing overflow.

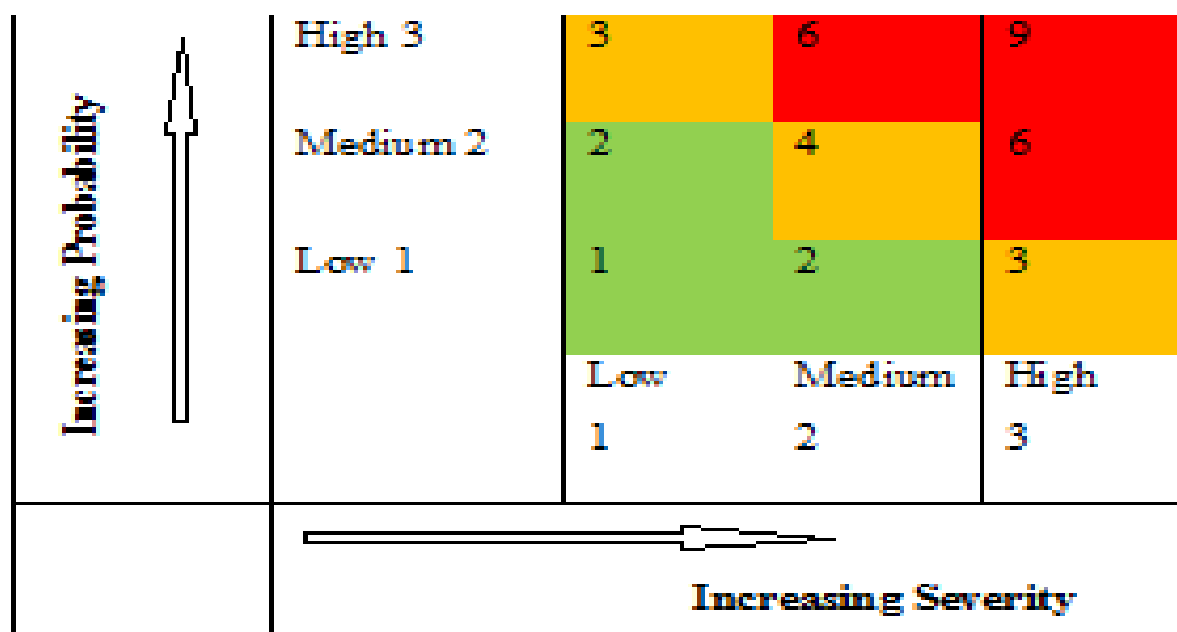


Fig. 4: Simple risk matrix

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). These regions can be shown in the matrix such as regions 6 and 9 for GU, regions 1 and 2 for GA and regions 3 and 4 for ALARP as shown in Fig.4.

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.

Technology Transfer Perspective: The enablers of pharmaceutical quality system, “knowledge management” and “quality risk management”, both play an operative role in implementing technology transfer^(8,9). QRM tools could be ably applied to prevent any possible damage to the quality of final product¹⁰. Furthermore, QRM is used as an

integral part of product development to assess critical attributes of raw materials, API, excipients, or packaging materials in designing quality product⁽¹¹⁾. QRM helps in identifying the “Critical Process Parameters” (CPP) and “Critical Material Attributes (CMA) which helps to determine whether any additional changes are required during scale-up⁽¹²⁾. QRM is important in every aspect of product development as it helps the manufacturer to control the potential risk to quality. Entailing control strategy in transfer ensures quality of finished product⁽¹³⁾. With QRM in technology transfer, the transfer process becomes robust and safeguards quality of final product. PIC/S Methodology of QRM: The method for quality risk management provided by PIC/S supports the global policy of risk management. Commonly followed way is to analyze risks of a particular step in the entire product life cycle and then divide it into elementary steps and apply the risk management process to each of the elementary step. Two levels of risk i.e. “primary risks” and “residual risks” together can be analyzed to know the risk minimization action to be taken. Primary risks are quantified initially by applying the risk treatment process to each elementary step. Controls are then taken following CAPA (Corrective Action and Preventive Action), internal information, external information, and periodic review. The output obtained is quantified in the form of residual risks. It depends on the mission of the company to what level it wants to minimize the risks in totality (For example; risk minimization up to 50%)⁽¹⁴⁾.

The principle followed in PIC/S methodology of QRM is based on the compatibility of the volume of resources with the possibilities of the organization. It follows a dissociating approach, separating the constants and variables of the risk management i.e. the system and product respectively. System means those items implemented by the organization like facilities, equipment, personnel, processes, etc., and the variables are different type of products manufactured by the plant. Risk

management process once applied to the constant is sufficient for one type of product which can be multiplied with specific product characteristics. The system becomes an existing one which is under permanent control after risks are evaluated and can be managed independent of the product. When the product is introduced later, this prevents duplication of systemic risk evaluation for different products manufactured. The global risk (R_g) then becomes the multiplication of systemic risk (R_s) the constant, and the product factor (P) the variable i.e., " $R_g = R_s \times P$ "

Quantitative analysis is based on parameters of systemic risk (R_s) i.e. Severity (S), Probability (P) and Detectability (D). As described previously with emphasis to implementation, the system risk will be equal to the multiplication of S , P and N , N being the experience gained by the organization on its systemic environment. Parameter D is not directly involved; it is taken as a conditional parameter to be used while making decision about the acceptance of the risk. The product factor (P) takes into account the experience gained by the organization with the product, called as component (E) and the intrinsic properties of the product, considered as component (C). This factor is calculated as a combination of component E and component C increased by 1.000. i.e., ($P = E + C + 1$).

" P " is increasing and monotonous, however, if taking a value of 1 for P , and then the global risk will be equal to the systemic risk only. The parameters described for components E and C is included considering the scientific literature and published results. For example: component ' E ' takes into account parameters like development or clinical phase of the product, number of occurrence for successful manufacturing of the product within the organization and origin of the product (API manufacturer, excipient manufacturer). The component ' C ' takes into account parameters associated with intrinsic properties of the product like; pharmacological and toxicological data (no observed adverse effect level, bioavailability, physiologically active dosage), physicochemical data (solubility, particle size distribution, density), therapeutic indication class, pharmacokinetics (plasma half-life in human) etc.

Need for improvisation of QRM practice: *Credit of using subjective scoring systems*: It is believed that ratings of severity, probability of occurrence and detectability are not assigned in an evidence based manner, for example; a high probability of occurrence is assigned based on detection of any subject i.e. if controls are in place to detect a subject then we can observe that the risk occurs frequently or less frequently. This means something can be detected but not prevented, something which is easily challenged by inspectors⁽¹⁵⁾.

Using QRM tools not designed for GMP use: QRM is intended to support good manufacturing practices, but it does not seem as such. The GMP controls put in place to assure product quality and regulatory compliance are not found to be effective even after applying risk based approaches. There is poor translation of risk assessment output to validation protocols, qualification programs and

change control proposals which indicates that there is somewhere a false proposal of security.

Lack of technicality in QRM activities: For example, failure modes are identified but on what basis are unclear. Whether the identified failure modes are the real ones for which risk action is to be taken is still not clear which ultimately results into ineffective root cause analysis for the real risk and thus ineffective risk control actions.

Dependence upon expert opinion: Present QRM environment is mostly about seeking expert opinion. But, this is not accountable in a GMP environment as the intuition used by the experts is not calculable, nor is their memory. Inclusion of qualified personnel into the QRM program is not in the lime light.

No method to measure the QRM work: This is a problem mostly in the qualitative approaches used in risk assessment. Improvements in the qualification and validation, risk reductions achieved and level of protection of patient cannot be known. A work with result seen or measured is only regarded useful; hence the pattern of QRM approach is to be improved.

CONCLUSION

A lot of work has been done on improving the quality of medicinal products and are 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. In terms of technology transfer QRM proved to be effective in reducing errors in transfer and concluding successful transfer. During this study, it is observed that there are serious quality defects which are on increase since 2004. Even though there are good harmonized guidelines available, its practice is difficult for many industries because of economic reasons. A few suggestions in this regard are 1) implementing the methodologies meant for training purposes developed by PIC/S, 2) taking help of real time cases studies of QRM and implementing it in the organization, and 3) gaining knowledge by understanding the process of one's own organization so that a company can implement a tailor made QRM process, that fits well for it. Implementation of the risk based cGMP should be made mandatory for all manufacturers including the generic players. Generic and biosimilar market-share forecast is very promising for the pharmerging countries like India^{16, 17, 18}. 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.

REFERENCES

1. The Wall Street Journal [Internet]. New Prescription For Drug Makers: Update the Plants. [Updated 2003

- Sep 3; Cited on 2012 Nov 23]; Available from: <http://online.wsj.com/article/SB10625358403931000.html>.
2. Lotlikar MV. Quality risk management (QRM): A review. *Journal of Drug Delivery & Therapeutics* [Internet]. 2013 [cited 2014 March 28]; 3(2): 149-54. Available from: <http://jddtonline.info/index.php/jddt/article/viewFile/447/269>
 3. Kevin O'Donnell. Improving Quality Risk Management Activities to better support GMP Activities. Irish Medicines Board [Internet] 2012 Sep [Cited on 2013 Feb 14]; Available from: <http://www.imb.ie/images/uploaded/documents/GMP%20info%20day%20presentations/4.1%20Improving%20Quality%20Risk%20Management%20activities%20to%20better%20support%20GMP%20Activities.pdf>.
 4. A Guide to Supply Chain Risk Management for the Pharmaceutical and Medical Device Industries and their Suppliers. [Internet] 2010 [Cited on 2012 Dec 27]; Available from: <http://www.thecqi.org/Community/Special-Interest-Groups-SIGs/Pharmaceutical-Quality-Group/PQG-guide/>
 5. 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 [Internet] 2008 Dec 28 [Cited on 2012 Dec 27]; Available from: http://www.pqri.org/pdfs/MTC/Quality_Risk_Management_Principles_and_Industry_Case_Studies_December_28_2008.pdf.
 6. EtQ's Webinar [Internet]. Risk Management 2.0 The expanding role of Risk Mitigation in Industries. [Updated 2012; Cited on 2012 Dec 22]. Available from: <http://online.wsj.com/news/articles/SB10625358403931000?mg=reno64-wsj&url=http%3A%2F%2Fonline.wsj.com%2Farticle%2FSB10625358403931000.html>
 7. Process Deviation – Empty Product Capsules. [Internet]. Manufacturing Technology Committee – Risk Management Working Group: Risk Management Case Studies. [Cited on 2012 Dec 27]. Available from: [http://www.pqri.org/pdfs/MTC/Case_Study_RMWG-08_Empty_Capsules_\(3\)_\(2\).pdf](http://www.pqri.org/pdfs/MTC/Case_Study_RMWG-08_Empty_Capsules_(3)_(2).pdf).
 8. Ildiko Mohammed-Ziegler, Ildiko Steff, Maria Halmaj-Varenyi. Importance of quality risk management in pharmaceutical quality systems: Recent trends and harmonization. *Saudi Pharm J* [Internet]. 2013 Dec 20 [cited 2014 March 28]. Available from: http://ac.els-cdn.com/S1319016413001473/1-s2.0-S1319016413001473-main.pdf?_tid=03e12fb2-b639-11e3-9bfb-00000aacb35e&acdnat=1395984354_4dac0295b3ee635a00ebb28d15ae58fc
 9. Dubey N, Gupta H, Sharma R.K, Dubey Nitin, Dubey Nidhi. Pharmaceutical Quality Management System: Current Concept. *Journal of Advanced Pharmacy Education & Research* [Internet]. 2011 [cited 2014 March 29]; 2: 120-24. Available from: <http://www.japer.in/Issue/Issu%20%20august/32.pdf>
 10. Jain Shashank. Quality By Design: A Comprehensive understanding of implementation and challenges in pharmaceutical development. *Int J Pharm Pharm Sci* [Internet]. 2013 Nov 07 [cited 2014 March 28]; 6(1): 29-35. Available from: <http://www.ijppsjournal.com/Vol6Issue1/8108.pdf>
 11. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [Internet]. ICH Harmonized Tripartite Guideline, “Quality Risk Management,” Q9 step 4, [updated 9 Nov 2005; cited 2014 March 26]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf
 12. Jones Robert. Pharmaceutical Manufacturing: How to understand the process and Assess the risks to patient safety. *Pharmaceutical Manufacturing and Product Quality* [Internet]. 2009 Nov/Dec [cited 2014 March 28]; 29(6): 1-10. Available from: <http://www.fwc.com/getmedia/01f7d46b-2ca6-41b6-8831-7ed8d1aa3f76/09ND-Jones.pdf.aspx?ext=.pdf>
 13. Little. A Thomas. Essentials in Quality By Design. Focus On Manufacturing [Internet]. 2014 March [cited 2014 March 31]; 12(3): 18-24. Available from: http://www.bioprocessintl.com/multimedia/archive/00231/BPI_A_141203AR03_O_231739a.pdf
 14. PIC/S [Internet]. Quality Risk Management – Implementation of ICH Q9 in the Pharmaceutical field an example of methodology from PIC/S. [Updated 2012; cited 2012 Dec 6]. Available from: http://www.picscheme.org/pdf/65_psinf012010exampl eofqrmimplementation-copy1.pdf.
 15. Irish Medicines Board [Internet]. Improving Quality Risk Management Activities to better support GMP Activities [updated 2012 Sept 27; cited 2013 June 6]; Available from: <http://www.imb.ie/images/uploaded/documents/GMP%20info%20day%20presentations/4.1%20Improving%20Quality%20Risk%20Management%20activities%20to%20better%20support%20GMP%20Activities.pdf>.
 16. Global Intelligence Alliance [Internet]. Latest insights: Emerging Markets. [Updated 2012; Cited on 2012 Dec. 27]. Available from: <http://www.globalintelligence.com/insights-analysis/emerging-markets/industryreports/pharmaceuticals-healthcare>.
 17. Report Linker [Internet]. Pharmaceutical Industry: Market Research Reports, Statistics and Analysis. [Updated 2012; Cited 2012 Dec. 27]. Available from: <http://www.reportlinker.com/ci02257/Pharmaceutical.html>
 18. Fierce Pharma Manufacturing [Internet]. Industry Voices: Investing in local manufacturing in emerging

markets, [updated 2012 Dec 12; Cited 2012 Dec. 27].
Available from:
<http://www.fiercepharmamanufacturing.com/story/in>

[dustry-voices-investing-local-manufacturing-emerging-markets/2012-12-11](#)