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How Quality Risk Management is Useful for Pharmaceuticals

Vivek P. Chavda[1]*, Sandip Maru[2], & Bhargav Patel[3]
[1]Department of Pharmaceutics, B.K. Mody Government Pharmacy College, Rajkot (India)
[2]Quality Assurance, Intas Pharmaceutical Ltd., Ahmedabad
[3]Quality Assurance, Zydus cadila pharmaceutical Ltd., Ahmedabad
*Author of Correspondence

Abstract

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. This review is grafted to provide potential applicability of QRM approach in pharma field. The examples are provided for illustrative purposes and only suggest potential uses of quality risk management. Now a day it becomes a integral part not even for pharmaceutical but also for its related consumables.

Keywords: *Risk management program, Quality risk management (QRM), Pharmaceutical industry*

1. 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. [1]

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. For any real-world system, there are an infinite number of tests that one can conceivably run. How does one choose the best possible subset? A smart approach would be to pick those tests that address the most important risks. Testing reduces risks to system quality. It helps identify areas of the system that work properly (that is, the tests pass). It also helps identify opportunities to make the system better (that is, the tests fail, detecting bugs). So smart test managers should ask, "How do we test the most critical areas and find the most critical bugs?"

2. QRM Applications in Pharmaceuticals: [1-7]

2.1 Training and education

Training of relevant personnel in industry, MRAs and universities in QRM principles and applications is essential for its effective implementation. Industry employees should understand what QRM is, possess the skills necessary to apply it properly, and have access to appropriate resources to enable the effective practice of the QRM principles. In developing the training programme to support QRM activities, working instructions and procedures should be drawn up which clarify the strategy and define the tasks of all personnel involved in these activities. Specific training should be provided as required to enhance awareness. Staff with the responsibility for managing and reviewing risks should receive formal training in the relevant procedures. Cooperation between producers, traders and responsible authorities is vital. Opportunities should be provided for the joint training of industrial staff and MRAs to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of QRM. The success of QRM depends on the education and training of management and employees to understand the importance of QRM in producing and supplying safe pharmaceuticals.

2.2 Responsibilities

Successful application of QRM is dependent on a clear understanding of responsibilities by all personnel involved in the QRM activities. It is recommended that a cross-functional matrix of assigned responsibilities and accountabilities is drawn up and shared with all relevant personnel. The pharmaceutical manufacturer should ensure that appropriate

knowledge and expertise are available for the effective planning and completion of QRM activities. QRM activities are usually, but not always, undertaken by a matrix of interdisciplinary teams. When teams are formed they should include experts from the appropriate areas (e.g. quality unit, product development, engineering, regulatory affairs, production operations, statistics, clinical, and others, such as sales, marketing or legal, as applicable), in addition to individuals who are knowledgeable about the QRM process. In this respect it is acceptable for external consultants to participate in the QRM matrix team where they can provide specific expertise or knowledge. Their role should be justifiable and clearly defined and the resultant accountability must be understood. A technical agreement or other equivalent document with the consultant may be appropriate where a GMP responsibility is assumed. Similarly, contract staff may become involved in leading or participating in risk assessments, e.g. a contract authorized person. The extent of their involvement and responsibility and accountability must be documented in a technical agreement or other equivalent document between the individual concerned and the pharmaceutical company. Regarding the authorized person it is important that a company's internal procedures are clear on where the responsibility lies for final approval of risk acceptance documents. Effective matrix team leadership is required to take responsibility for coordinating QRM across various functions and departments of the organization and to ensure that the QRM activities are adequately defined, planned, resourced, deployed and reviewed. The leader and team will need to identify critical resources required to implement the QRM activities, and also specify a timeline, deliverables and appropriate levels of decision-making for the QRM process.

2.3 QRM application during product development

The application of QRM procedures evolves through the various stages in the development of a product. The first QRM exercise should be performed once the QTPP is defined and preformulation work on the candidate medicine is complete. At this stage of a project there may be significant gaps in knowledge. Therefore, it will be important to apply risk tools that are appropriate for such a situation. These might include:

- ✓ cause and effect diagrams (also known as Ishikawa or Fishbone diagrams);
- ✓ flowcharts (e.g. input-process-output (IPO));
- ✓ decision-trees;
- ✓ fault-tree analysis;
- ✓ Relationship matrices.

As the product progresses to later stage of development, a more detailed analysis of the risks associated with both the active pharmaceutical ingredient (API) and the FPP should be considered. Risks would cover concerns associated with stability, bioavailability and patient safety including any challenges to these areas resulting from the manufacturing process (including, for example, API form conversion under certain conditions of processing). As product knowledge advances, more detailed QRM exercises can be considered, concentrating on areas considered to present higher priority risk. As the product's critical quality attributes (CQAs) become defined, the potential risks arising from each input material (API, excipients, any device or pack components) and each secondary product unit operation can be investigated. Eventually, for the developed FPP, the increasingly comprehensive risk assessment will support a thorough understanding of the product and will enable all key variables to be identified, understood and controlled.

2.4 QRM application during validation and qualification

In keeping with the principles of QRM, these guidelines recommend that process validation embraces the product life-cycle concept already mentioned. Accordingly, process validation activities should involve the generation and evaluation of data throughout the process, from development to full-scale production, which will provide a science-based assurance of consistent delivery of quality product in the production operation. It is important to emphasize that the building of scientific assurance begins early in development. It is obtained through rational design of experiments and robust evaluation of data during product and process development through to the commercial production phase, by which time the API and FPP CQAs are well understood and controlled. In this scenario, validation or (perhaps more appropriately termed) conformance batches serve to reinforce the science- or risk-based decisions that have been made as product development has advanced and should demonstrate good control of all critical sources of variability that have been identified. Any unplanned variations within a batch or between batches should be evaluated employing suitable statistical tools, e.g. trend analysis, to check on process control. A potential advantage of this approach is that there can be flexibility in the number of validation or conformance batches required for regulatory scrutiny prior to approval. The traditional number of batches required for validation has been three but, with QRM embedded in a product's development process, the number of conformance batches needed depends on the depth of knowledge about the process. For very low-volume products, e.g. orphan drugs, this may preclude the need to manufacture multiple batches. It would be beneficial for decisions of this nature regarding conformance batches to have an effective company–MRA dialogue to agree on requirements for a regulatory submission. When applicable, the principles of QRM should also be applied for qualification activities. QRM principles can be used to determine the scope of qualification. They can also be used to determine the optimal schedule for maintenance, monitoring, calibration and requalification. Manufacturers should have sufficient knowledge of the process and product to ensure that by the time the product is commercialized, processes are optimized and risks are minimized.

2.5 QRM application during commercial manufacturing

In general, implementing QRM should not obviate a manufacturer's obligation to comply with regulatory expectations (e.g. regulatory requirements, regulatory filings and inspection commitments). All QRM activities should be structured in a way that allows responsibility for risk assessment and actions at appropriate levels of the hierarchy within the organization. Special focus can be put on the risk assessment and risk control during the life-cycle of a product, and may include:

- ✓ product quality risks;
- ✓ adverse impact on patient health resulting from product quality defects;

- ✓ interruption of product supply to patients;
- ✓ GMP and regulatory compliance risks;
- ✓ multisite risks;
- ✓ multiproduct risks;
- ✓ New facility and changes to existing facility, e.g. start-ups, new commercial manufacturing processes, technology transfers and product discontinuation.

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

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

In principal, areas of focus when implementing QRM in commercial manufacturing include a system focus, a process focus and a product focus.

2.6 QRM integration with key quality system elements

Effective QRM can facilitate the decision on "What to do?" and, therefore, support better and more informed decisions. QRM should be integrated into existing quality system elements and related business processes and documented appropriately. Accordingly, the use of QRM can be beneficial across a broad spectrum of operations, e.g.:

- ✓ integrated quality management:

– Documentation
– Training and education
– Quality defects
– Auditing and inspection
– Change management and change control (includes equipment, facilities, utilities, control and IT systems)
– Continual improvement and corrective and preventive actions
(CAPA);

- ✓ facilities, equipment and utilities:

– Design
– Qualification
– Maintenance and decommissioning of facility or equipment
– Hygiene aspects
– cleaning of equipment and environmental control
– Calibration and preventive maintenance
– Computer systems and computer-controlled equipment;

- ✓ supplier, materials and contract service management:

– Assessment and evaluation of suppliers and contract manufacturers
– starting material
– Use of materials
– Storage
– Logistics and distribution conditions;

- ✓ technology transfer:

– From development to manufacturing
– During commercial manufacturing between sites
– From commercial manufacturing to product discontinuation.

2.7 QRM application in product manufacturing operations

Effective QRM can facilitate the "How to do it?" and, therefore, ensure that the products will meet acceptable standards for safety, quality, and compliance. Among others, QRM methodology can support the following actions to assess and control quality risks:

- ✓ production:

– manufacturing process risks
– validation
– In-process sampling and testing controls
– Production planning
– Deviation and investigation management
– change management;

- ✓ laboratory control and stability studies:

– Out-of-specification results
– retest period and expiry date
– Method transfers;

- ✓ packaging and labelling:

– Design of packages
– Selection of container-closure system
– label controls;

✓ storage, transport and distribution:
– e.g. cold chain.

2.8 Quality Risk Management as Part of Materials Management

✓ Assessment and evaluation of suppliers and contract manufacturers

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements).

✓ Starting material

To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

✓ Use of materials

To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing); To determine appropriateness of reprocessing, reworking, use of returned goods.

✓ Storage, logistics and distribution conditions

To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design); To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management) in conjunction with other ICH guidelines; To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance); To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

2.9 Quality Risk Management as Part of Laboratory Control and Stability Studies

✓ Out of specification results

To identify potential root causes and corrective actions during the investigation of out of specification results.

✓ Retest period / expiration date

To evaluate adequacy of storage and testing of intermediates, excipients and starting materials.

2.10 Quality Risk Management as Part of Packaging and Labelling

✓ Design of packages

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility).

✓ Selection of container closure system

To determine the critical parameters of the container closure system.

✓ Label controls

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label.

3. Conclusion

Quality Risk Management is a systematic process for evaluation, control, communication and review of risks to the quality of the drug product across the product lifecycle. 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.

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