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Review Article

QRM CONSIDERATIONS FOR MEDICINES REGULATORY AUTHORITIES

VIVEK P. CHAVDA*

Department of Pharmaceutics, B.K. Mody Government Pharmacy College, Near Aji dem, Rajkot-Bhavnagar highway, Gujarat technological university, Rajkot-360003, Gujarat (India) E-mail: vivek7chavda@gmail.com, Fax: 0281 – 2384279

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ABSTRACT

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. In regulatory perspective it is used to assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity. It is also helps evaluate the significance of products; like quality defects, potential recalls and inspectional findings. It is also find its potential; appropriateness and type of postinspection regulatory follow-up To identify risks that should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT)). In short QRM has become a mandatory regulatory requirement towards healthcare organizations.

KEYWORDS*:* Risk management program, Failure modes and effects analysis (FMEA), Pharmaceutical industry

INTRODUCTION

Since last few years Quality Risk Management (QRM) has become a mandatory regulatory requirement for Pharmaceuticals. 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 pertains scientific and practical decisions when integrated into quality systems, examples of quality systems include Validation, Quality Defects - Investigation, Auditing, Inspection, Documentation, Training etc. 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. A key principle of these guidelines is that all medicines regulatory authorities (MRAs), manufacturing sites in developing countries and API manufacturers should demonstrate, wherever appropriate, application of QRM throughout the product life-cycle for development and manufacturing facilities. Inspectors will review this QRM system as part of the quality systems section of the inspection (along with complaints, recalls, deviations, product quality reviews and others). Equally, it is recommended that QRM be applied by the MRAs themselves (reviewers and inspectorates) as there are clear benefits of a QRM-based review and inspection plan. For example, inspectors can allocate time and resources commensurate with the perceived significance of risk in any given situation and can be pragmatic regarding the level of scrutiny and degree of formality required.

QRM application to inspection strategy [1-5]

Risk management in inspections

The inspection section or unit of an MRA should operate within a written, implemented quality management system. SOPs should be followed for activities including (but not limited to) inspection planning, review of corrective and preventive actions after inspections and complaint handling and investigation. Where appropriate, the procedures and activities during inspection should be in line with the principles of QRM. The unit should have a risk management plan that describes the philosophy, approach, procedures and implementation of risk management. The risk management plan should be reviewed and updated on a continuous basis, or at least annually, and should cover all types of inspections

(including GMP, good clinical practices (GCP), good laboratory practices (GLP)) and other activities. Appropriate risk assessment tools should be used in the process, and the risk assessment for a site to be inspected should be documented on a risk assessment worksheet. Records should be maintained. A metric system should be used for risk ratings, e.g. on a scale from 1 to 3.

Inspection planning and conduct

The frequency and scope of inspections should be determined based on risk assessment that covers product risk and patient risk. Risk rating should normally be done only for sites that have been previously inspected. The risk assessment worksheet should be completed after every inspection. Inspection of a site that has not been inspected previously may be waived only in cases where a recognition procedure exists between regulatory inspection units, and where, in addition, appropriate evidence of GXP compliance is available which indicates that there is no risk or an acceptably low risk to products and patients. Various factors should be considered in the risk assessment exercise, and these factors may be different for the different types of GXP inspections. Risk factors to be considered depend on the type of inspection, and may include:

Outcome of inspection by another regulatory authority;

Outcome of the previous inspection;

Complexity of the site (e.g. buildings, utilities);

Complexity of the product (e.g. sterile, non-sterile); type of product (e.g. biological, low-dose); complaints and recalls;

Significance of changes (e.g. equipment, key personnel);

Results of product testing;

Risk to the patient;

Complex route of synthesis (API);

Polymorphism (API);

Biopharmaceutical classification of the product;

Innovative or emerging technology.

Risk rating of the site of inspection will be considered for determining number of inspectors and number of days required for the inspection, as well as the scope of the inspection. Based on findings and observations risk report should be prepared. It can be categorized as “critical”, “major” or “minor”. The unit should have an SOP that describes the classification process. Classification should be based on risk assessment. The level of risk assigned should be in

accordance with the nature of the observation as well as the number of occurrences.

Corrective action and preventive action (CAPA) review, and scheduling of routine inspections

CAPA should be requested from a site, following an inspection. The CAPAs should address the observations included in an inspection report. Based on the outcome of the inspection and the acceptability of the CAPA, the risk rating of the site should be reviewed and recorded. Inspection frequency should be defined based on the risk rating. For example, the frequency can be defined as every 6, 12, 18 or 24 months. (*Note*: The maximum time interval should be no more than every 36 months.)

Complaint handling and investigation

Handling and investigation of quality complaints should be done in accordance with a written SOP. The scope and depth of the investigation (including whether a desk review or on-site inspection will be done) should be based on risk assessment.

Inspection of QRM at a manufacturing site

During inspections, inspectors should assess whether a manufacturer has appropriate skills and scientific knowledge, as well as product and process knowledge, for the QRM procedure being inspected. This is also relevant where a company has made use of contracted parties. The company's QRM procedure should be appropriately detailed and should be integrated into the company's quality management system. It should cover at least the following areas:

- It should specify the general approach to both planned and unplanned risk assessment, including scope, responsibilities, controls, approvals, management systems, applicability and exclusions.
- Personnel should have appropriate qualifications, experience and training. Their responsibilities with regard to QRM should be clearly defined.
- Senior management should be involved in the identification and implementation of QRM principles within the company.
- The risk management procedure(s) for each area of application should be clearly defined.
- Quality assurance principles should be applied to QRM-related documentation, e.g. review, approval, implementation and archiving. QRM policies and procedures should be clear and the workflow should be systematic and conducted in a logical order.
- The procedure for risk management should be implemented.
- Manufacturers should identify significant risks and consider all the relevant data from reliable sources.
- The level of effort and resources used in risk assessment should be appropriate to the importance of the identified problem.
- Critical issues should be addressed with appropriate urgency and formality.
- There should be a logical selection of tools for risk assessment.
- Risk acceptance criteria should be appropriate.
- Risk assessments should not underrate the severity, nor overrate detection of occurrences resulting in underestimating patient risk.
- The risk acceptance criteria should be appropriate for the specific situation in question.
- Risk controls should be effective.
- The company should have a review programme to measure the effectiveness of the measures taken.
- Risk-based decision(s) should be science-based and concordant with the predefined acceptance criteria.
- All documentation related to the QRM activities should be completed within a reasonable period and should be accessible.
- Risk assessments performed should be reviewed when appropriate, and additional controls implemented when required.
- Personnel should be trained and assessed in the principles of QRM.
- Where appropriate, a team of members of personnel should participate in the QRM processes.

QRM applied to dossier review (assessment)

The assessment processes of national medicines regulatory authorities (NMRAs) rely on QRM principles in the management of resources (time and assessors), as well as in the management of product-related risk factors. Efficient management of resources minimizes the risk that limited resources are not used to their best effect, and ultimately ensures that important products are made available in a timely manner. Key factors to be considered include the prioritization of dossiers, the screening process, identification of the specific risk factors inherent to a given dossier or dosage form, and allocation of resources to the various sections of a dossier for a given product. In addition, product-related risk factors must be managed throughout the life-cycle of the product, for example, through effective communication between assessors and inspectors, and by establishing systems for dealing with the products after approval. The allocation of priority to dossiers should take into account the therapeutic needs of the regional population (e.g. disease occurrence, the need for paediatric formulations, combination products, or experience with innovative or emerging technology) and the availability of medicines on the market. Prioritization should be a dynamic process to enable it to accommodate emerging issues such as pandemics. Other considerations related to prioritization based on medical need may include fixed-dose combinations versus single-ingredient or co-packaged products, extended release products versus products administered as two or three daily doses, second-line versus first-line products, flexible dosage forms such as dispersible tablets and variable dose products such as oral liquids. The screening process examines the completeness of a dossier. Screening ensures that only those dossiers that meet minimum standards for completeness can enter into the full assessment process. Insufficient screening processes allow lower quality dossiers to be accepted for review, thus significantly increasing assessment time. Identification of dossier-related and product-related risk factors allows for the allocation of appropriate resources to specific dossiers. Possible risk factors include: the experience and track record of the manufacturer, narrow therapeutic range products, sterile versus non-sterile APIs and products; API-related considerations such as use of semi-synthetic and fermentation products, complex routes of synthesis, polymorphism, isomerism and potential genotoxic impurities; and product-related considerations such as the use of novel excipients, the complexity of the formulation, single-ingredient versus fixed-dose combinations, and special delivery systems (e.g. modified release, transdermal products, and inhalation products). Once risk factors have been identified, resources should be allocated to minimize risk. For example, assessors with expertise related to the product-related risk identified should be assigned to assess the dossier whenever possible. When resources allow, the assessors may be organized according to specialization, assigning assessors to various product categories (e.g. generic products, sterile products, solid oral dosage forms, or special delivery systems). This can facilitate the development of expertise in key areas and promote consistency of review, as well as ensuring that products requiring specialized knowledge are identified and assessed by those with the appropriate expertise. Where a high level of risk is identified for a dossier, the more experienced assessors need at least to be available on a consultation basis. The risk level associated with a dossier may change during the course of assessment. For example, rejection of the bioequivalence study will result in additional time required to conduct and assess additional studies and associated additional quality information. In such a scenario the risk relates both to the use of additional resources and to an increased risk that the overall product quality may be poor.

Allocation of resources to various aspects or sections of the dossier is an important QRM consideration, in order to ensure that the resources used are commensurate with the risk level. An understanding of the relative criticality of dossier sections or aspects is necessary for efficient use of resources. All aspects of the dossier are important to achieve overall quality, safety and efficacy; however some areas are inherently more critical from a risk perspective and

warrant more attention in the assessment process. Examples include the clinical reviews bioavailability reviews, API synthesis, specifications and stability studies, FPP manufacturing details, pharmaceutical development studies including biowaiver justification, process validation, specifications and stability studies. An example applicable to most simple solid oral products is that more time should be allocated to the review of manufacturing steps prior to packaging than to reviewing the packaging process. During the assessment process there should be a standard procedure for communicating to the inspectors those issues identified which may require consideration during inspection. After approval of a product, QRM principles should be applied to evaluate the impact of proposed variations or changes. Clear guidelines that outline possible post-approval changes and assign an associated risk level are an effective means to achieve this.

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