WHO GUIDELINE ON
QUALITY RISK MANAGEMENT

REVISED DRAFT FOR DISCUSSION

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We will now send out our working documents electronically and they will also be placed on the Medicines web site for comment. If you do not already receive our draft specifications please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.

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SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/10.376: WHO GUIDELINE ON QUALITY RISK MANAGEMENT

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<td>First draft points for consideration prepared by Dr Simon Mills, UK</td>
<td>May 2010</td>
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<td>Review of initial draft points in informal consultation on quality assurance systems, medicines and risk analysis</td>
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<td>Discussion during informal consultation on WHO quality risk management and quality guidelines</td>
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[Note from Secretariat: During the informal consultation held on 28-30 June 2011, it was suggested that the WHO Expert Committee members should consider that the implementation of the general principles included in this guideline could be rather short; however, regarding the full implementation of the system and the application of the related tools, this would necessitate a longer timeframe. The QRM approach was considered by all experts to be a very important part of quality assurance in the future.]
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1.  INTRODUCTION

1.1  Background and scope
In most countries compliance with good manufacturing practices (GMP) (1, 2) (including validation), drug regulatory activities and inspections, together with supply chain controls throughout the product life-cycle, provide good assurance that risks are largely controlled. However, where control is less effective, patients may be put at risk through the production of medicines of inadequate quality. The assessment of individual risks related to specific products and starting materials and the recognition of hazards at specific stages of production or distribution should permit regulatory authorities to improve control of medicines by increasing the effectiveness of their activities within the limits of the available resources. Quality risk management (QRM) is a process that is relevant to all countries and should provide a rationale to understand risk and mitigate it via appropriate and robust controls.

The aim of this guideline is to assist the development and implementation of effective QRM covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing, storage and distribution. In the past, hazard analysis and critical control point (HACCP) methodology, traditionally a food safety management system but subsequently applied to other industries, has been the basis of WHO risk management guidance to the pharmaceutical industry (3).

Since then international guidance has emerged (2, 5-8) that is of specific relevance to the pharmaceutical industry and which addresses the full scope of pharmaceutical industry QRM more effectively than HACCP principles, including how to structure regulatory filings using a risk-based approach. Consequently, this WHO guideline has been developed as an update of WHO advice to the pharmaceutical industry, taking account of this new guidance.

In order to protect patients, in terms of quality, safety and efficacy, international medicines regulatory authorities (MRAs) are recommending pharmaceutical manufacturers to adopt a risk-based approach to the life-cycle of a pharmaceutical product. Some MRAs are requiring the adoption of a risk-based approach for certain specific areas in the life-cycle of a pharmaceutical product, e.g. for environmental monitoring for sterile products manufacturing.

While the choice of the tools to support the QRM approach is optional and may vary, they need to be appropriate for the intended use.

In return for using this approach, there are potential opportunities for both MRAs and pharmaceutical manufacturers (4) as summarized in the following sections.

a) Quality risk management (QRM) principles can be applied to both MRAs and pharmaceutical manufacturers:

- **MRAs:** systematic and structured planning of reviews and inspections that are risk-based. The submission review and inspection programmes can also operate in a coordinated and synergistic manner.

- **Manufacturers:** design, development, manufacture and distribution, i.e. the life-cycle of a pharmaceutical product. QRM should be an integral element of the pharmaceutical quality system (QRS).

b) Science-based decision-making can be embedded into QRM processes:

- **MRAs:** decisions regarding review, inspection or inspection frequency should consider product risk and GMP compliance of the manufacturer. The MRA accepts residual risks through understanding the QRM decisions involved.
Manufacturers: quality decisions and filing commitments can be based on science-based process understanding and QRM (when utilizing the quality by design approach). Its effective application should offer manufacturers greater freedom on how to meet principles of GMP, and this, therefore, should encourage innovation. The control strategy for the process focuses on critical quality attributes and critical process parameters. Uncertainty can be addressed explicitly.

c) Resources can be focused on risks to patients:

MRAs: QRM can be used to determine best allocation of inspection resource, both in terms of product types and for specific areas of focus for a given inspection. This enables the most efficient and effective scrutiny of the most significant health risks. Those manufacturers with poor histories of GMP compliance can also be more closely and frequently evaluated by on-site inspection than those manufacturers with better records.

Manufacturers: evaluation of quality risk through science-based decisions can be linked ultimately to protection of the patient by ensuring the quality, safety and efficacy of the product. A corporate culture is supported to produce cost-effective medicines, without compromising quality, while maintaining focus on the patient as a primary stakeholder in all activities.

d) Restrictive and unnecessary practices can be avoided:

MRAs: regulatory scrutiny adjusted to level of risk to patients. Improvement and innovation by manufacturers should be encouraged.

Manufacturers: instead of having systems designed to inhibit change and minimize business risk, changes can be managed within a company’s quality management system. Innovation and the adoption of the latest scientific advances in manufacturing and technology are supported. Unnecessary testing can be eliminated, for example, with real-time release testing.

e) Communication and transparency are facilitated:

MRAs: facilitate dialogue with pharmaceutical manufacturers and clarify to the industry and the public on how the inspection programme may be adjusted based on the risk to patients. Information-sharing between MRAs will contribute to a better risk management approach globally.

Manufacturers: matrix team approach, stakeholders kept informed via science-based decisions. Culture of trust and “one-team” mindset with focus on product and patient.

QRM is the overall and continuing process of appropriately managing risks to product quality throughout its life-cycle in order to optimize its benefit/risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

This guideline will align with the general framework described within other current international guidance on this subject.
1.2 Principles of quality risk management

The two primary principles of QRM are:

- evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient; and
- the level of effort, formality and documentation of the QRM process should be commensurate with the level of risk.

Beside these the following principles are also part of the QRM methodology:

- when applied, processes using QRM methodologies should be dynamic, iterative and responsive to change; and
- the capability for continual improvement should be embedded in the QRM process.

This guidance describes the WHO approach to QRM, using the concepts described in ICH Q9 and illustrated in Figure 1 (reproduced from ICH Q9). 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.

Figure 1. Overview of a typical quality risk management process

![Diagram of quality risk management process](image-url)

Taken from reference 6: ICH Q9: Quality Risk Management. This figure is also available on the ICH website [www.ich.org](http://www.ich.org).

Decision points are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based...
upon information that supports such a decision. Note: “unacceptable” in the flowchart does not only refer to statutory, legislative or regulatory requirements, but also indicates that the risk assessment process should be revisited.

The approach described in this guideline should be used to:

- systematically analyse products and processes to ensure the best scientific rationale is in place to improve the probability of success;
- identify important knowledge gaps associated with processes that need to be understood to properly identify risks;
- provide a communication process that will best interface with all relevant parties involved in the QRM activities;
- facilitate the transfer of process knowledge and product development history to ease product progression along the life-cycle and to supplement already available knowledge about the product; and
- enable the pharmaceutical industry to adopt a risk-based approach to development as described in external regulatory guidance (5-8). The QRM outputs will potentially serve as reference documents to support product development and control strategy discussions in regulatory filings.

Early in development, the purpose of the QRM process is to acquire sufficient product and process knowledge to assess risks associated with formulation development of the finished pharmaceutical product (FPP) according to the quality target product profile (QTPP). In recognizing risks and knowledge gaps, the QRM process plays a significant role in proactively enabling the prioritization and mitigation of risks. The objective is to develop the FPP through maximizing product and process knowledge and risk mitigation.

As FPP development progresses, in addition to supporting that development, the purpose of the QRM process is to determine and manage risks to bioavailability, safety, efficacy and product quality. QRM in development should differentiate process parameters (PPs) and quality attributes (QAs) from critical process parameters (CPPs) and critical quality attributes (CQAs), thereby contributing to the defining and refining of the control strategy.

The long process of product development is inevitably complex and requires the continual exchange of data, decisions and updates both internally within companies and, where required with external stakeholders, such as MRAs. A very important aspect of product development and QRM is the maintenance of an effective and secure knowledge management and documentation system. Such a system must facilitate transparent communication and the highlighting of key issues to stakeholders and also possess a well-structured archive. Clearly, the ability to organize diverse data and information effectively and then retrieve it as required for updating and further evaluation, for the purposes of process validation as an example, would be hugely beneficial.

Finally, it should be noted that QRM activities are focused on the product/process development and product manufacturing, ultimately to ensure a robust, safe and effective FPP. The existence and effectiveness of the relevant aspects of good clinical practices (GCP), good laboratory practices (GLP) and GMP should also be assessed when performing QRM activities.
2. QRM PROCESS

2.1 Initiating a QRM process

QRM activities should be performed using systematic processes designed to coordinate, facilitate and improve science-based decision-making with respect to risk. Possible steps used to initiate and plan a QRM process might include the following (Ref ICH Q9):

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

2.2 Personnel involved in QRM

The implementing party, i.e. pharmaceutical manufacturer or regulatory authority, should assure that personnel with appropriate product-specific knowledge and expertise are available to ensure effective planning and completion of QRM activities. This may be best accomplished by assembling a multidisciplinary team according to guidance in section 3.2. The personnel should be able to:

(a) conduct a risk analysis;
(b) identify and analyse potential risks;
(c) identify, evaluate risks and determine which ones should be controlled and which ones can be accepted;
(d) recommend and implement adequate risk control measures;
(e) devise procedures for risk review, monitoring and verification.

The objectives and scope of the QRM activities should be clearly defined. The scope should describe the segment of the process involved.

2.3 Knowledge of the product and process

Any activity of QRM would need to be based on knowledge of the product or processes concerned, according to the stage of the product life-cycle.

Where necessary, a flow diagram may be helpful, covering all operations and controls in the process under evaluation. When applying QRM to a given operation, the steps preceding and following that operation should also be considered. A block-type diagram may be sufficiently descriptive. Amendments to the flow diagram may be made where appropriate, and should be documented.

2.4 Risk assessment (3)

When risk assessment is conducted safety and efficacy need to be considered in addition to the quality concerns.
During the assessment all the risks that may be reasonably expected to occur in the activity under evaluation should be listed. This is usually applied during its initiation when there is a change or a concern and may also be applied to existing processes. An analysis should be conducted to identify which risks are of such a nature that their elimination or reduction to acceptable levels is essential.

A thorough risk analysis is required to ensure an effective risk control. It should review the materials, activities, equipment, storage, distribution and intended use of the product. Typically a list of the potential risks (biological, chemical and physical) which may be introduced, increased or controlled in each step should be drawn up. In the risk analysis the following basic questions should be addressed:

- What is the nature of possible risks?
- What is the probability of their occurrence and how easy is it to detect them?
- What are the consequences (the severity)?

It should then be decided which potential risks should be addressed by the QRM activities and what control measures, if any, should be implemented for each risk. If a risk has been identified at a step where control is necessary for safety, and no control measure exists at that step or at any other, the product or process should be modified at that step, or at an earlier or later stage, to include such a control measure. More than one control measure may be required to control a specific risk and more than one risk may be controlled by a specified control measure.

Options for risk assessment methodologies are described in section 5.

Risk assessment can be facilitated by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned, e.g. production, packing, reprocessing, storage or distribution. The best use of QRM tools is discussed further in section 5 of this guidance.

Normally, potential risks in relation to the following should be considered:

- materials and ingredients;
- physical characteristics and composition of the product;
- processing procedures;
- microbial limits, where applicable;
- premises;
- equipment;
- packaging;
- sanitation and hygiene;
- personnel – human error;
- utilities; and
- supply chain.

The output of a risk assessment is either a quantitative estimate of risk (numeric probability) or a qualitative description of a range of risk (e.g. high/medium/low) and may be related to a risk matrix (see section 5). The scoring system and trigger points for mitigating action are subjective so the rationale for score categorization should be defined in as much detail as possible. If supported by factual evidence it should be more obvious what mitigating action is required – the mitigating action is as important as the score assigned. Professional
judgement should be used in interpretation of factual evidence but must be subject to justification.

Records of risk assessments should be maintained according to the document management system (see also 2.8).

The expectation of QRM is to assess risks to the product quality and to the patient and then manage these risks to an acceptable level. It is appropriate for companies to assess their control systems to implement the optimum controls to ensure product quality and patient safety. Risk assessment and mitigation in order to achieve cost savings but which could be to the detriment of the patient is an unacceptable practice (9).

2.5 Risk control

Risk control is a decision-making activity designed to reduce and/or accept risks. It usually occurs after risk assessment, and at a fundamental level its purpose is to reduce the risk to an acceptable level.

During risk control activities the following key questions should be asked:

- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk control activities usually involve identifying controls and measures which may reduce or control the risk associated with a failure mode or negative event. Risk control activities can serve to determine critical process parameters for certain controls, how they will be monitored, and the level of qualification and validation which may be required, if any, for such controls.

If risk assessments are conducted and risk controls are employed they should be documented, subject to change control. If conducted for an ongoing activity it should be subject to periodic review and the frequency of review should be appropriate for the nature of the activity.

Specific corrective actions should be developed to prevent recurrence of instances where there have been deviations from established risk control measures, especially for high risks. These actions should ensure that the risk is brought under control as soon as possible in compliance with the established deviation handling procedures.

Specific corrective actions should be developed in advance for each identified risk including what is to be done when a deviation occurs, who is responsible for implementing the corrective actions, and that a record will be kept and maintained of the actions taken.

2.6 Risk review

Appropriate systems should be in place to ensure that the output of the QRM process is periodically monitored and reviewed, as appropriate, to assess new information that may impact on the original QRM decision. Examples of such changes include changes to control systems, changes to equipment and processes, changes in suppliers or contractors and organizational restructuring.
Monitoring is the scheduled measurement or observation of a specific risk control measure relative to its acceptance limits. Monitoring should be recorded.

All records and documents associated with risk review should be signed and dated by the person(s) carrying out the review and by a responsible official(s) of the quality unit of the company.

2.7 Verification of QRM process and methodologies

The established QRM process and methodologies need to be verified. Verification and auditing methods, procedures and tests, including random sampling and analysis, can be used to determine whether the QRM is working appropriately. The frequency of verification should be sufficient to confirm the proper functioning of the QRM process.

Verification activities include:

(a) review of the QRM process and its records;
(b) review of deviations and product dispositions; and
(c) confirmation that identified risks are kept under control.

Initial verification of the planned QRM activities is necessary to determine whether it is scientifically and technically sound, that all risks have been identified and that, if the QRM activities are properly completed, these risks will be effectively controlled.

Information reviewed to verify the QRM process should include:

(a) expert advice and scientific studies; and
(b) in-plant observations, measurements and evaluations.

Subsequent verifications should be performed and documented by a QRM team or an independent expert, as needed. For example, verifications may be conducted when there is an unexplained system failure, a significant change in product, process or packaging occurs or new risks are recognized. Where possible verification should include actions to confirm the efficacy of all elements of the QRM activities.

In addition, a comprehensive review of the QRM process and specific instances of QRM application by an independent third party may be useful. This would include a technical evaluation of the risk analysis and each element of the QRM process and its application as well as an on-site review of all flow diagrams and appropriate records of the operation of the QRM activity. Such a comprehensive verification is independent of other verification procedures and should be performed in order to ensure that the QRM process is resulting in the control of the risks. If the results of the comprehensive verification identify deficiencies the QRM process should be modified as necessary.

Individuals doing verification should have appropriate technical expertise to perform this function.

2.8 Risk communication and documentation

Communication of the QRM process should include key stakeholders. By ensuring that key stakeholders are engaged in both the data collection process for the risk assessment and the decision-making for risk control, this will ensure commitment and support for the QRM. The
output of the QRM process and associated risk analysis justifying the approach should be documented and endorsed by the organization’s quality unit and management. Additionally, this information should be communicated to stakeholders for their information and to ensure their support.

There should be a report for every risk assessment, but the level of effort, formality and documentation will commensurate with the level of risk (2).

Regarding conclusions to a risk assessment the mitigation controls should minimize the likelihood of risk to patient safety to an acceptable level of assurance, on the understanding that no risk whatsoever is unlikely in reality. The degree of risk tolerated very much depends on the circumstances, the proximity to the patient and other controls that might follow the process being assessed before the product reaches the patient (2). It is expected that risk mitigation plans are identified and implemented where any risk to patient safety is posed. Companies should take the holistic view and be mindful that critical issues often arise where multiple failures in systems occur together so mitigation plans should be sufficiently robust to cover this scenario. Inspectors will assess if risk assessments underrate the likelihood of occurrence and consequences of overrating detection such that the patient risk is underestimated. The factual evidence behind statements should be robust to challenge by inspectors.

All risk assessments performed by an organization should be documented for the purposes of inspection. This should list and track all key risks as perceived by the organization and summarize how these have been mitigated. There should be a clear reference to risk assessments and a list of risk assessments conducted should be maintained. A management process should be in place to review QRM – this may be incorporated into the quality management review process.

3. QRM APPLICATION FOR PHARMACEUTICALS

3.1 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 be appropriately resourced 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 involved in these activities. Specific training should be provided as required to enhance awareness. Staff who have responsibility for managing and reviewing risks should receive formal training in the relevant procedures.

Cooperation between producers, traders and responsible authorities is of vital importance. 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 educating and training of management and employees in the importance of QRM in producing and supplying safe pharmaceuticals.
3.2 Responsibilities

Successful application of QRM is dependent on a clear understanding of responsibilities for all staff 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. For example, one may consider the use of techniques such as RACI (Responsibility/Accountability/Consulted/Informed) grids to illustrate a more complete picture of the communication pathways.

The pharmaceutical manufacturer should assure 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 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 to lead or participate in risk assessments, e.g. a contract authorized person. The extent of involvement and responsibility/accountability must be documented in a technical agreement or other equivalent document between the individual 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 their organization and ensuring that the QRM activities are adequately defined, planned, resourced, deployed and reviewed. The leader and team will need to identify critical resources to progress the QRM activities, and also specify a timeline, deliverables and appropriate levels of decision-making for the QRM process.

3.3 QRM application during product development

The application of QRM procedures evolves through the various stages in development of a product.

It is important to, where possible, identify risks in the early phases of product development that could challenge the achievement of the QTPP. The first QRM exercise should be performed once the QTPP is defined and preformulation work on the drug candidate is complete. For 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; and
• relationship matrices.

As the product progresses to later stage development, a more detailed analysis of the risks associated with both the API and FPP becomes a requirement. Risks would cover concerns associated with stability, bioavailability and patient safety including any challenges to these 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 be 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.

3.4 QRM application during validation and qualification

In keeping with the principles of QRM, this guideline recommends 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 development process into full-scale production that will provide a science-based assurance of consistent delivery of quality product in the production operation (12, 13, 14).

An important emphasis is 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/process development through to the commercial production phase at which time the API and drug product CQAs are well understood and controlled. In this scenario, validation or (perhaps more appropriately termed) conformance batches just 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 identified critical sources of variability. Any unplanned variations within a batch or between batches should be evaluated accordingly, 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 that needs to be made 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. Until new approaches to demonstrate validation mature and become widely used, the traditional three-batch approach to validate a process is still acceptable.

When applicable the principles of QRM should also be applied for qualification activities.
Qualification includes four stages (design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)) but most frequently, only IQ, OQ and PQ are performed by manufacturers. QRM principles can be used to narrow the scope of IQ, OQ and PQ to cover only the essential elements that can affect product quality. It can also be used to determine the optimal schedule for maintenance, monitoring, calibration and requalification.

Most importantly, by the time that a product is ready for commercialization, the manufacturing company will be expected to have derived sufficient knowledge of the commercial production process to support that commercialization to the optimized benefit of and minimized risk to the patient.

3.5 QRM application during commercial manufacturing

[Note from the Secretariat: text to follow.]
4. QRM CONSIDERATIONS FOR MEDICINES REGULATORY AUTHORITIES  

QRM should be applied by the MRAs (reviewers and inspectorates). Both the MRA should have a standard operating procedure (SOP) integrated with its quality system.

4.1 Inspection strategy

It is a requirement that regulatory inspections cover the QRM process of the organization in question. QRM, along with GMP and quality control (QC), should be considered as a key pillar of what must be a comprehensively designed and correctly implemented system of quality assurance (QA).

4.1.1 Application of a QRM methodology

All marketing authorization holders, FPP and active pharmaceutical ingredient (API) manufacturing sites should demonstrate, wherever appropriate, application of QRM throughout the product life-cycle for development and manufacturing facilities. Inspectors will review the QRM processes as part of the quality systems section of the inspection (along with complaints, recalls, deviations, product quality reviews, etc.), if applicable. Additionally, inspectors may review specific risk assessments when encountered during the course of an inspection. Inspectors can allocate time and resources commensurate with their perceived significance of the risk and, only if necessary, request the organization to produce a formal summary of the risk assessment, key decisions and conclusions or take risk-assessment details for further evaluation outside the inspection. Inspectors should be pragmatic regarding the level of scrutiny and degree of formality required for any given situation.

4.1.2 Standard operating procedures

The inspected organization should have SOPs integrated with its quality system that define how the management system operates and its general approach to both planned and unplanned risk assessment. It should include scope, responsibilities, controls, approvals, management systems, applicability and exclusions.

4.1.3 QRM deficiencies

QRM deficiencies are quality systems deficiencies, as there is an expectation that QRM should be an integral part of the QMS and may be grouped with other quality systems deficiencies.

4.2 Inspection activities

Inspectors should expect inspected companies to demonstrate that appropriate skill, scientific knowledge, product and process knowledge and accountabilities were appropriate for the QRM procedure being inspected. This might be of particular relevance and concern where a company has made use of consultants and contractors. The following subsections provide inspection guidance in highlighting typical areas for scrutiny.
4.2.1 Inspection of the QRM methodologies (11)

a) Integration of QRM into the company’s quality management system:
   - the areas of application of QRM should be appropriately defined in the company's quality management system;
   - there should be appropriate personnel with relevant 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; and
   - quality assurance principles should be applied to QRM-related documentation, e.g. review, approval, implementation and archiving.

b) QRM procedures:
   - the workflow in relation to QRM activities should be systematic and conducted in a logical order;
   - there should be a logical approach to selection of methods and tools supporting a company’s QRM activities;
   - the procedure for definition of risk acceptance criteria must be adequate, for example, involving personnel having appropriate expertise to understand all aspects of the evaluation;
   - risk assessments should not underrate the likelihood, consequences nor overrate detection of occurrences such that the patient risk is underestimated. Consider challenging the factual evidence behind statements; and
   - if the financial impact on the inspected organization is reported as a potential impact in a risk assessment, it must be ensured that this is not to the detriment of the patient.

4.2.2 Inspection of individual risk-based decisions (11)

The following QRM methodology and activities should be considered:
   - the documented internal QRM and quality system procedures should be adhered to;
   - the risk question/problem should have been clearly defined;
   - appropriate training needs to be implemented for all the personnel involved (fully or in part) in the QRM activity, and who in total should have the appropriate combined expertise to address the question/problem defined;
   - all relevant stakeholders should have participated at an appropriate level in the QRM procedure;
   - there should be a logical approach to selection of methods and tools supporting the risk-based evaluation and a systematic approach applied to the implementation of the QRM activities;
significant risks should have been adequately identified and analysed, with all relevant data having been generated and/or considered. All data reviewed should be from a reliable source. The risk acceptance criteria need to be adequate for the specific situation in question;

- the risk-based decision(s) must be considered to be well-informed, science-based and comprehensible. They must be concordant with the pre-set acceptance criteria;

- the level of effort and resources deployed in the QRM activity should be proportionate to the importance of the identified problem. Critical issues should have been addressed with appropriate urgency and formality and risk-based decisions made by decision-makers with appropriate competence and authority;

- the risk-reduction measures resulting from risk-based evaluations and decision(s) must demonstrate the required effect. The company should have adopted a suitable review programme to evaluate the outcome of the measures; and

- all documentation related to the QRM activities should have been completed in a reasonable time frame and should be accessible to relevant staff and retrievable at the time of inspection.

4.3 QRM in dossier review (assessment)

[Note from the Secretariat: text to follow.]
5. RISK MANAGEMENT TOOLS

A variety of tools can be used for the purposes of QRM, either alone or in combination. It is important to note that no single tool or combination of tools is applicable to every situation in which a QRM procedure is used. Examples of tools are listed in regulatory guidance (6, 8); neither list is exhaustive. The important criterion for acceptability is that the tool or tools are used effectively to support the key attributes of a good risk assessment.

The Product Quality Research Institute (PQRI) Manufacturing Technology Committee (MTC) has produced a summary (10) of common RM principles and best practices, several working tools to foster consistency in the use of ICH Q9 (6) in day-to-day RM decision-making, and a series of examples of RM applications currently in use by major pharmaceutical firms. They have also produced very helpful risk tool training modules for risk ranking and filtering, failure modes effects analysis (FMEA), hazard operability analysis (HAZOP) and HACCP (10) (add reference to examples listed.. ) and check for copyright

One aspect worth highlighting is the development of a risk matrix to facilitate categorization of identified risks during the risk assessment phase. In order to prioritize a risk, it is essential to agree upon its significance. The risk associated with any situation or event can be represented as the impact of that event multiplied by the probability of its occurrence; in other words, how likely is it to happen and how severe would it be if it did happen. Impact and probability can each be classified, e.g. into 5 levels (1-5) or with a weighting towards the higher probability and impact ratings (e.g. 1,3,5,7,10, etc.), so that a grid or matrix can be constructed.
Table 1. An example of a probability versus impact matrix

<table>
<thead>
<tr>
<th>Probability</th>
<th>Negligible</th>
<th>Marginal</th>
<th>Moderate</th>
<th>Critical</th>
<th>Catastrophic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost certain</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Likely</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Possible</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Unlikely</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Rare</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

The shading in the table represents an example of how the risk values (sometimes called composite risk indices or risk index values) can be assigned a high, medium or low status. The definition for each status should be predetermined in the QRM process after consideration of the specific consequences for the process undergoing risk assessment. These consequences can be split according to the probability and impact scores, as exemplified in Table 2.

Table 2. Example of a consequences table for probability and impact

<table>
<thead>
<tr>
<th>Score</th>
<th>Probability</th>
<th>Example</th>
<th>Score</th>
<th>Impact</th>
<th>Consequence</th>
</tr>
</thead>
</table>
| 1     | Rare        | • Seen every 10-30 years | 1     | Negligible | • No regulatory issue  
• No effect on and not noticeable by patient |
| 2     | Unlikely    | • Seen every 5-10 years | 2     | Marginal  | • May require MRA notification  
• Decision to release product not compromised |
| 3     | Possible    | • Seen every 1-5 years | 3     | Moderate  | • MRA inspection may identify a major concern but deficiency quite easily resolved  
• Limited product recall possible |
| 4     | Likely      | • Seen to occur more than once a year | 4     | Critical  | • MRA inspection may conclude serious non-compliance  
• Likely product recall from one or more markets |
| 5     | Almost certain | • Seen several times a year | 5     | Catastrophic | • Enforcement action by MRA such as consent decree, product seizure  
• Global product recall |

This table is just a very basic example and would need to be customized for the specific process in question to enable better and practical definition of the consequence categories. It should be cautioned that the value of a risk matrix does very much rely upon input information and should only be used by staff with a good understanding of the embedded judgements and, as such, the resolution of low/medium/high categorization.
As a summary of the common, well-recognized QRM tool options available for the purposes of this guideline, the following table has been based on the one from the PQRI-MTC report.\(^\text{10}\) The list is not comprehensive but it does include some of the more frequently used approaches.

### Table 3. Examples of common risk management tools (based on 10)

<table>
<thead>
<tr>
<th>Risk management tool</th>
<th>Description/attributes</th>
<th>Potential applications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic tools</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagram analysis</td>
<td>• Simple techniques that are commonly used to gather and organize data, structure RM processes and facilitate decision-making</td>
<td>• Compilation of observations, trends or other empirical information to support a variety of less complex deviations, complaints, defaults or other circumstances</td>
</tr>
<tr>
<td>• Flowcharts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Check sheets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Process mapping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cause/effect diagrams</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk ranking and filtering</td>
<td>• Method to compare and rank risks</td>
<td>• Prioritize operating areas or sites for audit/assessment</td>
</tr>
<tr>
<td>• Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk score</td>
<td>• Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool</td>
<td></td>
</tr>
<tr>
<td><strong>Advanced tools</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fault tree analysis (FTA)</td>
<td>• Method used to identify all root causes of an assumed failure or problem</td>
<td>• Investigate product complaints</td>
</tr>
<tr>
<td>• Used to evaluate system or subsystem failures one at a time, but can combine multiple causes of failure by identifying causal chains</td>
<td>• Evaluate deviations</td>
<td></td>
</tr>
<tr>
<td>• Relies heavily on full process understanding to identify causal factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard operability analysis (HAZOP)</td>
<td>• Tool assumes that risk events are caused by deviations from the design and operating intentions</td>
<td>• Access manufacturing processes, suppliers, facilities and equipment</td>
</tr>
<tr>
<td>• Uses a systematic technique to help identify potential deviations from normal use or design intentions</td>
<td>• Commonly used to evaluate process safety hazards</td>
<td></td>
</tr>
<tr>
<td>Hazards analysis and critical control points (HACCP)</td>
<td>• Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring</td>
<td>• Better for preventative applications rather than reactive</td>
</tr>
<tr>
<td>• Bottom-up approach that considers how to prevent hazards from occurring and/or propagating</td>
<td>• Great precursor or complement to process validation</td>
<td></td>
</tr>
<tr>
<td>• Emphasises strength of preventative controls rather than ability to detect</td>
<td>• Assessment of the efficacy of CPPs and the ability to consistently execute them for any process</td>
<td></td>
</tr>
<tr>
<td>• Assumes comprehensive understanding of the process and that critical process parameters (CPPs) have been defined prior to initiating the assessment. Tool ensures that CPPs will be met.</td>
<td>(continued)</td>
<td></td>
</tr>
</tbody>
</table>
Failure modes 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; analyse a manufacturing process to identify high risk steps and/or critical parameters

6. **GLOSSARY**

**Control strategy** (source: ICH Q8)
A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10).

**Critical quality attribute (CQA)** (source: ICH Q8)
A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

**Finished pharmaceutical product (FPP)**
The finished pharmaceutical product always represents a pharmaceutical product after final release (manufacturing control release, quality control release, packaging control release).

**Formal experimental design** (source: ICH Q8)
A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “design of experiments”.

**Pharmaceutical product**
Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.
Pharmaceutical product target profile (PPTP)
A definition of the target properties of the FPP, including dosage form and strength(s), route of administration and relevant drug release and pharmacokinetic requirements

Planned risk assessment
An assessment that is conducted in advance of an activity, either before any work is conducted or before further work is conducted. This enables quality to be built into activities and risk reduced, e.g. design of high containment facilities for manufacture of cytotoxic products.

Process robustness (source: ICH Q8)
Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

Product quality research institute (PQRI)
A collaborative process involving the United States Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER), industry and academia. The mission of PQRI is to conduct research to generate specific scientific information that should be submitted in a regulatory filing to CDER (but which will be worth consideration for all MRAs). PQRI member organizations, representing industry, academia, and government, cover a wide array of scientific issues related to pharmaceutical products. Through its working groups and technical committees, PQRI tackles projects to ensure the quality, safety and performance of drug products and produces publications for the public domain based upon the output of those projects.

Qualification
Action of proving and documenting that any premises, systems and equipment are properly installed and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

Quality critical process parameter (source: ICH Q8)
A process parameter whose variability has an impact on a critical quality attribute and, therefore, should be monitored or controlled to ensure the process produces the desired quality.

Stakeholder
Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Primary stakeholders are the patient, healthcare professional, MRAs and the pharmaceutical industry.

Unplanned risk assessment
An assessment that is conducted to assess the impact of a situation that has already occurred, e.g. impact of a deviation from normal ways of working.

Validation
The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes-including equipment, buildings, personnel and materials are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do.
Verification
The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the quality risk management activities.

7. REFERENCES


