World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO guidelines on quality risk management

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25 SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/26.994:

26 # WHO guidelines on quality risk

27 # management

Description of activity	Date
Preparation of first draft working document.	April - May 2026
Review and finalization of the first draft working document with an informal drafting group.	June – July 2026
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	September - November 2026
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	December 2026 – January 2027
Discussion of the feedback received on the working document in a virtual meeting with an informal drafting group.	February 2027 - April 2027
Discussion of the feedback received on the working document in a virtual meeting with an informal consultation group.	June - July 2027
Preparation of a working document for discussion and possible adoption by the ECSPP.	July – September 2027
Presentation to the sixty-first meeting of the ECSPP.	October 2027
Any other follow-up action as required.	

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1 Introduction

In most countries compliance with good manufacturing practices (GMP)(1), medicines 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.

Quality risk management (QRM) is a process that is relevant to all countries and should provide a rationale to understand risk and mitigate it through appropriate and robust controls.

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.

To protect patients in terms of quality, safety and efficacy of medicines, international medicines regulatory authorities (MRAs) are recommending pharmaceutical manufacturers to adopt a risk-based approach to the life-cycle of a pharmaceutical product.

The level of QRM activity and the density of associated documentation will evolve as the product progresses from early development through to routine production.

QRM is the overall and continuing process of appropriately managing risks to product quality throughout the product's 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 pharmaceutical product. It can be applied both proactively and retrospectively.

The application of digitalization and emerging technologies in the manufacture and control of pharmaceutical products can lead to risk reduction, when such technologies are fit for their intended use. However, they can also introduce other risks that may need to be controlled. The application of quality risk management to the design, validation and technology transfer of advanced production processes and analytical methods, advanced data analysis methods and computerized systems is important. but remember that validation requirements for these technologies should not be overlooked (2).

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The aim of these guidelines 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.

Effective and proactive quality risk management can enable better, more informed and timely decisions throughout the lifecycle. This can provide regulators with greater assurance of a company's ability to deal with potential risks and avert problems and can beneficially affect the extent and level of direct regulatory oversight (2).

Quality risk management should not be used in a manner where decisions are made that justify a practice that would otherwise, in accordance with regulations and/or guidance, be deemed unacceptable. While the choice of the tools to support the QRM approach is optional and may vary, the tools chosen need to be appropriate for the intended use.

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

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 quality management system

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.
- Manufacturers: quality decisions and filing commitments can be based on a science-based understanding of the process and QRM (when using the quality by design approach, and other approaches where appropriate). Its effective application should offer

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manufacturers greater freedom to decide how to comply with the principles of GMP and this, therefore, should encourage innovation.

Resources can be focused on risks to patients:

- MRAs: QRM can be used to determine the best allocation of inspection resources, 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 the focus on the patient as a primary stakeholder in all activities.

Restrictive and unnecessary practices can be avoided:

- MRAs: regulatory scrutiny should consider the 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, wherever needed

Communication and transparency are facilitated:

- MRAs: facilitate dialogue with pharmaceutical manufacturers and communicate clearly to the industry and the public 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 are kept informed through science-based decisions. This builds a culture of trust and a “one-team” mindset with a focus on the product and the patient.

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1.1 Scope

The aim of these guidelines is to assist the development and implementation of effective QRM throughout products life -cycle such as research and development, sourcing of materials, manufacturing, packaging, testing, storage, distribution, submission/review processes, the inspection, and market surveillance and control of active pharmaceutical ingredients, pharmaceutical ,biological and biotechnological products((including the use of raw materials, solvents, excipients, packaging and labelling materials in pharmaceutical, biological and biotechnological products).

1.2 Principles of quality risk management

An understanding of formality in quality risk management may lead to resources being used more efficiently, where lower risk issues are dealt with via less formal means, freeing up resources for managing higher risk issues and more complex problems that may require increased levels of rigour and effort. Formality in this context refers to the degree of rigor and effort that are applied to the quality risk management approach. An understanding of formality can also support risk-based decision-making, where the level of formality that is applied may reflect the degree of importance of the decision, as well as the level of uncertainty and complexity which may be present. Formality in quality risk management is not a binary concept (i.e. formal/informal); varying degrees of formality may be applied during quality risk management activities, including when making risk-based decisions. In this way, formality can be considered a continuum (or spectrum), ranging from low to high.

The two primary principles of QRM are that:

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

In addition to the two principles above, the following principles are also part of the QRM methodology:

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

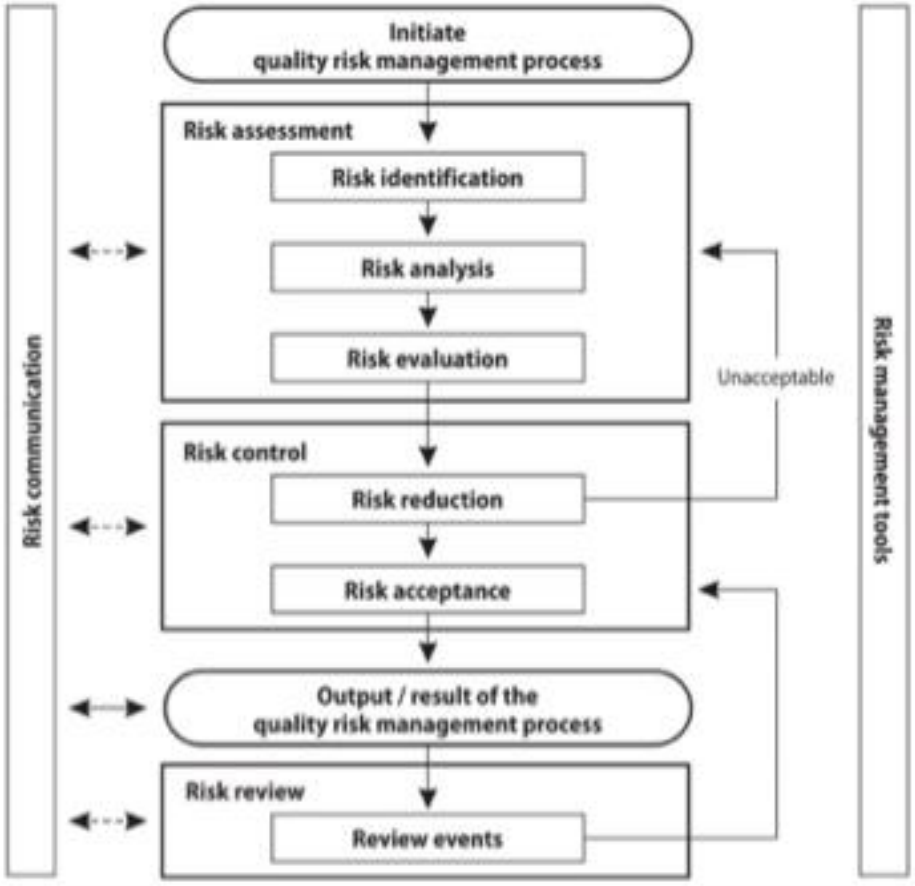
This guidance describes the WHO approach to QRM, using the concepts described in ICH Q9 (R1) (2) and illustrated in Figure 1. The emphasis on each component of the framework might differ from case

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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



Decision points are not shown in the diagram above because decisions can occur at any point in the process. The decision might be:

- to return to the previous step and seek further information;
- to adjust the risk models; or even
- to terminate the quality risk management process based upon information that supports such a decision.
- Unacceptable in the flowchart refers not only to non-compliance with statutory or regulatory requirements, but also indicates the need to revisit, refine, and, where

necessary, implement additional risk control measures within the quality risk assessment process.

The approach described in these guidelines may be used to:

- systematically analyse products and processes to ensure that 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 the 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 throughout its life-cycle and to supplement already available knowledge about the product;
- enable the pharmaceutical industry to adopt a risk-based approach to development as described in regulatory guidance (2–4). 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 may be 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 and quality attributes from critical process parameters (CPPs) and critical quality attributes (CQAs), thereby contributing to defining and refining the control strategy.

The 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 crucial aspect of product development and QRM is the maintenance of

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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 must also include a well-structured and accessible archive. Clearly, the ability to organize diverse data and information effectively and then retrieve them as required for updating and further evaluation, e.g. for the purposes of process validation, 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.

2 Glossary

control strategy: 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 active pharmaceutical ingredients (APIs) and finished pharmaceutical product (FPP) materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

critical quality attribute (CQA): 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.

failure mode: different ways that a process or subprocess can fail to provide the anticipated result.

failure mode, effects and criticality analysis (FMECA): a systematic method of identifying and preventing product and process problems.

finished pharmaceutical product (FPP): a finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

formal experimental design: 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”.

occurrence: probability of negative events within a fixed time frame.

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pharmaceutical product: any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

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 to be reduced, e.g. design of high containment facilities for manufacture of cytotoxic products.

process robustness: ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

qualification: the 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: a process parameter which could have an impact on the critical quality attribute.

quality risk management: a systematic process for the assessment, control communication, and review of risks to the quality of the pharmaceutical product across the product life-cycle.

risk: combination of the probability of occurrence of harm and severity of the harm.

risk analysis: the estimation of the risk associated with the identified hazards.

risk assessment: a systematic process of organizing information to support a risk decision to be made within a risk management process. it consists of the identification of hazards and the evaluation of risk associated with exposure to those hazards.

risk communication: the sharing of information about risk and risk management between the decision-maker and other stakeholders.

risk evaluation: the comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

risk identification: the systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

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risk priority number (RPN): a numeric assessment of risk assigned to a process, or steps in a process, as part of failure mode effects analysis (fmea). each failure mode gets a numeric score that quantifies likelihood of occurrence, likelihood of detection and severity of impact. the product of these three scores is the rpn for that failure mode. rpn = severity rating × occurrence rating × detection rating.

risk review: review or monitoring of output or results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

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, health-care 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 documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

verification: the application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the quality risk management activities.

3 Quality risk management process

3.1 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. The possible steps to be taken in initiating and planning a QRM process might include the following (2):

- 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 the necessary resources;

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- specify a timeline, the deliverables, and an appropriate level of decision-making for the risk management process.

Internal SOPs should define steps, stakeholders, roles and responsibilities (governance and management responsibilities).

3.2 Personnel involved in QRM

The implementing party, i.e. the 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. Senior management should be involved in the implementation of QRM principles within the company) according to the guidance provided in section 4.2. See section 5 for guidance in relation to the application of QRM by regulatory authorities.

The personnel appointed should be able to:

- conduct a risk analysis;
- identify hazards and analyse their potential risks;
- evaluate risks and determine which ones should be controlled and which ones can be accepted;
- recommend and implement adequate risk control measures;
- devise procedures for risk review, monitoring and verification;
- consider the impact of risk findings on related or similar products and/or processes.

QRM activities should be defined and documented.

3.3 Knowledge of the product and process

QRM should be based on knowledge of the product or processes concerned, according to the stage of the product life-cycle. See section 3.9 Managing and minimizing subjectivity in relation to the use of knowledge in risk assessment to manage and minimise subjectivity in the outputs of QRM activities.

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

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diagram may be made where appropriate, and should be documented.

For further information on knowledge management see ICH Q10 guideline on Pharmaceutical Quality System, section knowledge management (5).

3.4 Risk assessment

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 reasonably be expected to occur when conducting the activity under evaluation should be listed. This is usually done when the risk assessment is made for the first time, i.e. initiated, when there is a change or a concern and may also be applied to existing processes. An analysis should be conducted to identify which risk is essential to eliminate where possible, if not to reduce to an acceptable level.

A thorough risk assessment is required to ensure effective risk control. Risk assessment should review the materials, operations, 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 area should be drawn up. In the risk assessment the following basic questions should be addressed:

- What might go wrong?
- 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 of the potential risks should be addressed by the QRM activities and what control measures, if any, should be taken for each risk. If a hazard

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.

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Risk assessment can be aided 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, packaging, reprocessing, storage or distribution. The best use of QRM tools is discussed further in section 5.

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

- materials (ingredients, packaging materials, reagents, etc);
- physical characteristics and composition of the product;
- processing steps;
- microbial limits, where applicable;
- premises;
- equipment;
- packaging;
- sanitation and hygiene; environment;
- personnel (human error);
- utilities;
- 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 the score and trigger action are 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 interpreting the factual evidence but must be subject to justification. One useful strategy to reduce the extent of subjectivity in risk ratings and risk assessment outputs is to formally take into the account the controls that are in place which may impact a) the consequences of hazards, b) the probability of occurrence of the failure mode or hazard, and c) the level of detectability of the issue. In addition, the effectiveness of those controls is important to also assess. This approach can provide an evidence-basis for the risk ratings that are assigned during risk assessment activities.

Records of risk assessments should be maintained.

The expectation of QRM is to assess risks to the product quality and to the patient and then manage these risks so that they are kept at an acceptable level. It is appropriate for manufacturers to assess

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their control systems so as to implement the appropriate controls to ensure product quality and patient safety. An important principle in QRM is to design risks out of the process or eliminate such risks prospectively, whenever practical and feasible. Risk assessment and mitigation to achieve cost savings, but which could be detrimental to the well-being of the patient is unacceptable (*6*).

3.5 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 between benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk control can include:

- not proceeding with the risky activity;
- taking the risk; in order to follow an opportunity, or in case there are no controls available, or controls do not sufficiently modify the risk;
- removing the risk source;
- changing the likelihood of the risk;
- changing the consequences of the risk;
- sharing the risk with another party (e.g. contractor);
- retaining the risk by informed decision.

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, if any, which may be required for such controls.

If risk assessments are conducted and risk controls are employed, they should be documented. If the risk assessment is 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.

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Based on the criticality or level of risk, 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 and who is responsible for implementing the corrective actions. A record should be kept and maintained of the actions taken.

3.6 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 and 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.

3.6.1 Recording and Reporting

The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions

The risk management process and its outcomes should be documented and reported to provide information for decision-making, improve risk management activities. assist interaction with stakeholders. Reporting should include, but are not limited to:

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- differing stakeholders and their specific information needs and requirements.
- cost, frequency, and timeliness of reporting.
- method of reporting.

For further guidance, see ISO 31000:2018 on Risk Management (7)

It is useful to plan for Risk Review activities using a two-stage approach. Stage 1 is a planning stage; it is one of the outputs of the QRM process. Considerations here could include:

- Whether a Risk Review exercise needs to be performed on the process/item/area that was risk assessed.
- Whether any specific things should be reviewed during the Risk Review – e.g., the probability of occurrence of hazard X, or, the level of detection that a particular control has in relation to Risk Y, or, the degree of risk reduction that Control Z provided following its implementation.
- Whether any assumptions were made during the risk assessment – this is so that the validity of those assumptions can be checked during Risk Review.
- The areas where there were high levels of uncertainty or subjectivity during the risk assessment – this is so that these areas can be followed up on during Risk Review.

Stage 2 is the review of any new knowledge gained since the earlier Risk Assessment was performed, and the application of that knowledge to update the earlier Risk Assessment. Such new knowledge may relate to increased process experience, increased process understanding, learnings made during change controls, deviations, complaint investigations, etc. This knowledge can be used to define areas that may need to be improved (8)

3.7 Verification of QRM process and methodologies

Once in production, the QRM documentation can be integrated into the quality system and used to provide input into the product process.

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

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whether the QRM process is working appropriately. The frequency of verification should be sufficient to confirm the proper functioning of the QRM process.

Verification activities include:

- review of the QRM process and its records;
- review of deviations and product dispositions (management control);
- confirmation that identified risks are being kept under control.

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

Information reviewed to verify the QRM process should include:

- expert advice and scientific studies;
- 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, when 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 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.

3.8 Risk communication and documentation

Communication of the QRM process should include key stakeholders. Engaging the key stakeholders in both the data collection process for the risk assessment and the decision-making for risk control

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will ensure their commitment and support for the QRM. The output of the QRM process and associated risk analysis justifying the approach taken should be documented and endorsed by the organization's quality unit and management. Additionally, this information should be communicated to stakeholders to keep them informed and to ensure their support.

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

Regarding conclusions of 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 in response to the process being assessed before the product reaches the patient. It is expected that risk mitigation plans will be developed and implemented wherever 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 whether risk assessments underrate the likelihood of occurrence and the 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. The documentation should list and track all key risks as perceived by the organization and summarize how the risks 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.

3.9 Managing and minimizing subjectivity

This section is based on the ICH Q9(R1) guideline on Quality risk management (2).

Subjectivity is an element that can greatly influence the outcome of Quality Risk Management (QRM) activities and therefore can have a direct impact on the product quality and patient safety.

Subjectivity in QRM arises from personal opinions, biases, heuristics, or inconsistent interpretations of risks by stakeholders. This can impact every stage of the QRM process, from hazard identification

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to risk evaluation and mitigation. while subjectivity cannot be entirely eliminated, it can be controlled through structured approaches.

Subjectivity often stems from poorly designed scoring systems, differing perceptions of hazards and risks among stakeholders, and cognitive biases. To mitigate these challenges, organizations must adopt robust strategies that prioritize scientific knowledge and data-driven decision-making.

Reducing subjectivity in QRM is an ongoing process that requires a commitment to continuous improvement. Organizations should regularly review their QRM practices to identify areas for enhancement and incorporate feedback from stakeholders. Investing in training programs that build competencies in risk assessment methodologies and decision-making frameworks is essential for sustaining progress.

3.9.1 Strategies to Reduce Subjectivity.

Leveraging Knowledge Management: knowledge management as a tool to reduce uncertainty and subjectivity in risk assessments. By integrating knowledge management into QRM, organizations can ensure that decisions are based on comprehensive data rather than subjective estimations. When details related to historical trends, process validation data, lifecycle knowledge and prior investigations are integrated into QRM activities, subjectivity in QRM outputs is reduced as a result of the knowledge that is utilised to inform the risk assessments.

Develop Data Analytics Capabilities: Invest in data analytics tools and capabilities to extract meaningful insights from historical data. E.g. (Use statistical process control to identify trends in manufacturing performance, apply machine learning algorithms to predict potential quality issues based on historical patterns). These analytics can provide objective, data-driven insights into potential risks and their likelihood of occurrence.

Foster a Knowledge-Sharing Culture: Encourage a culture of knowledge sharing and collaboration within the organization, by promoting knowledge sharing, organizations can tap into the collective expertise of their workforce to improve risk assessments.

Implementing Structured Risk-Based Decision-Making: Organizations should establish clear criteria for decision-making processes, define acceptable risk tolerance levels, and use evidence-based methods to evaluate options. Structured decision-making tools can help standardize how risks are assessed and prioritized. Additionally, calibrating expert opinions through formal elicitation techniques can further reduce variability in judgments.

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3.10 Risk-based Decision-making

The use of knowledge during risk-based decision-making is of paramount importance to achieve informed risk-based decisions, trigger re-evaluations and stimulate continual improvements.

Robust knowledge management ensures that relevant knowledge is accessible on demand to those performing risk assessments and related quality risk management activities (such as risk reviews and making risk-based decisions). This helps ensure that quality risk management outputs are informed by the best available knowledge and that any new knowledge generated via quality risk management activities is captured and available for future use. In this regard, knowledge is both an input to, and an output of, quality risk management activities.

It is important to note that increased knowledge may also reveal previously unrecognised hazards, weaknesses in the current control strategy, or higher levels of residual risk than previously thought. These issues, if they arise. do need to be addressed. The correct application of knowledge during quality risk management activities ultimately leads to a better understanding of risk, more effective control strategies, and risk-based decisions that are easier to explain and defend.

Effective risk-based decision making is characterised by the following:

- It is informed by the best available knowledge about hazards, risks, and the effectiveness of risk controls. Such knowledge includes not only what is explicitly documented, but also experience and know-how (often referred to as 'tacit' knowledge).
- When risk assessment methodologies and tools are used to arrive at risk-based decisions, these are designed to minimise subjectivity and variability in their outputs, through the use of objective data and evidence, where available.
- Assumptions made during the decision-making process are explicitly documented and communicated, and they are also reviewed when new knowledge becomes available.
- As the importance of the decision increases, so too does the degree of rigour and effort that are spent ensuring the relevancy of the data and knowledge that are compiled to support the decision-making process. Likewise, an adequate degree of rigour and effort are spent analysing all available decision options.
- Decision criteria are agreed in advance, where possible, so that decisions are not driven mainly by preference, availability of data, hierarchy or convenience, but are informed by

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knowledge and a careful analysis of assumptions, uncertainties, risk controls and other important factors.

- The rationale for the final decision is documented in a way that shows how knowledge, assumptions, uncertainties, risk controls and other decision criteria were considered. This is particularly important where the decision relates to an area of high consequence, complexity, uncertainty, novelty, and when the decision is difficult to reverse, once made.
- New knowledge generated during the quality risk management and decision-making activity is captured and made available for future risk reviews, similar products and processes, and related decisions. This feed-back of new knowledge can lead to updated control strategies, revised procedures, enhanced monitoring methods, better training, as well as more informed triggers for future risk reviews.

Poor risk-based decision making is characterised by the following:

- An insufficient use of knowledge informs the decisions that are made.
- There is a high level of subjectivity in the risk assessment methodologies that lead to risk-based decisions.
- Assumptions are not clearly documented or communicated.
- Too little rigour and effort are spent analysing the data and knowledge requirements of the decision-making process, and, for decisions of high importance, all available decision options are not properly considered.
- Decision criteria are unclear, or they are introduced after a preferred option has already emerged.
- New knowledge generated during quality risk management activities is not captured or used to inform future activities and decisions, the organisation fails to learn from its decisions, and similar decisions are repeatedly made from a weak knowledge base.

4 QRM application for pharmaceuticals

4.1 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,

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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 and should be appropriately assessed to ensure effective application of quality risk management principles in practice.

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.

4.2 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

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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 clearly defined, appropriately planned, adequately resourced, effectively deployed and periodically reviewed. The designed 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.

4.3 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 pre-formulation 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)

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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.

4.4 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 (*6,9*).

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 CQAs of API and FPP are well understood and controlled. In this scenario, validation or (perhaps more appropriately conformance) batches serve to reinforce the science- or risk-based decisions adopted during the product development and should demonstrate high level of control of all critical sources of variability that have been identified. Any unplanned intra-batch or inter-batches variations should be evaluated employing suitable statistical tools, e.g. trend analysis, to assess and confirm the state of 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.

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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.

4.5 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.

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

4.5.1 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

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- during commercial manufacturing between sites
- from commercial manufacturing to product discontinuation.

4.5.2 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.

5 QRM considerations for medicines regulatory authorities

5.1 Introduction

A key principle of these guidelines is that all 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

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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 (for examples see (10)) 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 level of risk in any given situation and can adopt a pragmatic approach regarding the level of scrutiny and degree of formality required. For further guidance also consult the *WHO guideline on the implementation of quality management systems for national regulatory authorities (11)*.

5.2 QRM application to inspection strategy

5.2.1 Risk management in inspections

The inspection section or unit of an MRA should operate within a documented, implemented quality management system (*11*). 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 applicable, the procedures and activities during inspection should be in line with the principles of QRM.

The unit should have a documented 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 documented approach should be used for risk ratings, e.g. quantitative and/or qualitative.

5.2.2 Inspection planning and conduct

The frequency and scope of inspections should be determined based on risk assessment that covers product quality 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

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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 conducted by another regulatory authority;
- outcome of the previous inspection;
- complexity of the site (e.g. buildings, utilities);
- complexity of the process/product (e.g. sterile, non-sterile, route of synthesis);
- type of product (e.g. biological, low-dose);
- complaints and recalls;
- significance and frequency of changes;
- results of product testing;
- risk to the patient;
- polymorphism (API);
- biopharmaceutical classification of the product;
- innovative or emerging technology.

The number of inspectors and number of days required for the inspection, as well as the scope of the inspection, should be determined based on the risk rating of the site inspection.

Inspection reports should contain findings and observations. Any deviation from GXP should be classified, where appropriate, as “critical”, “major” or “other”. 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 commensurate with the nature of the observation as well as the frequency of its occurrences.

5.2.3 Corrective action and preventive action 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.

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Inspection frequency should be defined based on the risk rating. For example, the frequency can be defined as every 12, 18 or 24 months. (*Note*: The maximum time interval should be no more than every 48 months.)

For further guidance consult the Guidance on good manufacturing practices: inspection report (12).

5.2.4 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.

Note: This guideline does not address the application of Quality Risk Management to pharmacovigilance (adverse reactions) complaint reports, except in cases where the product which is associated with the adverse events needs to be specifically investigated from a quality perspective.

5.3 Inspection of QRM at a manufacturing site

Note: 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 requirement 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.

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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 readily available for review. Risk assessments performed should be reviewed when appropriate, and any additional control measures implemented when required.

Personnel should be trained and assessed in the principles of QRM. Where appropriate, a cross-functional team should be involved in the QRM-related processes.

5.4 QRM applied to dossier review (assessment)

The assessment processes of MRAs 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

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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 therapies versus first-line treatments, availability of flexible dosage forms such as dispersible tablets or variable dose products such as oral liquids. The screening process examines the completeness of each dossier. Screening ensures that only those dossiers that meet minimum standards for completeness can be accepted for the full assessment process. Inadequate screening procedures may result in the acceptance of lower-quality dossiers for review, thus significantly increasing assessment time. The screening of dossiers is important because low-quality dossiers may be an indication of poorly defined and controlled manufacturing processes where high levels of product variability could be the result. This has the potential to lead to product availability risks in cases where the manufacturing controls are not fit for purpose.

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-derived products, complex routes of synthesis, polymorphism, isomerism and potential presence of 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 formulations, transdermal products, and inhalation products). Once risk factors have been identified, appropriate resources should be allocated to minimize risks. For example, assessors with expertise related to the identified product-related risks should be assigned to to the evaluation of the dossier, whenever possible. When resources allow, the assessors may be organized according to specialization, assigning assessors to specific product categories (e.g. generic products, sterile products, solid oral

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dosage forms, or special delivery systems). This can facilitate the development of expertise in key areas and promote consistency in the review, as well as ensuring that products requiring specialized knowledge are identified and assessed by personnel 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 inadequate.

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 approach to achieve this objective.

For further guidance consult the Good review practices: guidelines for national and regional regulatory authorities (13).

6 Risk management tools

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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. It is important therefore, that the organization develops competency in using different risk management tools. Examples of tools are listed in regulatory guidance (*4*); 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 (*6*) of common risk management principles and best practices, several working tools to foster consistency in the use of ICH Q9 (*2)* in day-to-day risk management decision-making, and a series of examples of risk management 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) (*14*–*17*), hazard operability analysis (HAZOP) (*18*) and HACCP (*19*).

One aspect worth highlighting is the development of a risk matrix to facilitate categorization of risks identified 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).

Table 1

An example of a probability versus impact matrix

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	Impact				
Probability	Negligible	Marginal	Moderate	Critical	Catastrophic
Almost certain	5	10	15	20	25
Likely	4	8	12	16	20
Possible	3	6	9	12	15
Unlikely	2	4	6	8	10
Rare	1	2	3	4	5

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997 The shading in the table represents an example of how the risk values (sometimes called composite
998 risk indices or risk index values) can be assigned a high, medium or low status. The definition for each
999 status should be predetermined in the QRM process after consideration of the specific consequences
1000 for the process undergoing risk assessment. These consequences can be split according to the
1001 probability and impact scores, as exemplified in Table 2.

1002 Table 2

1003 **Example of a consequences table for probability and impact**

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Score	Probability	Example	Score	Impact	Consequence
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

MRA, Medicines regulatory authority.

This table is a very basic example and would need to be customized for the specific process in question to enable a better and more practical definition of the consequence categories. It should be cautioned that the value of a risk matrix relies very heavily upon input information and should only be used by staff with a good understanding of the embedded judgements and, as such, the resolution of the low, medium or high categorization.

As a summary of the common, well-recognized QRM tool options available for the purposes of these guidelines, Table 3 has been based on the one from the Product Quality Research Institute Manufacturing Technology Committee (PQRI-MTC) report (*6*). The list is not comprehensive, but it does include some of the more frequently used approaches.

Table 3

Examples of common risk management tools

Risk management tool	Description, attributes	Potential applications
Tools		
Diagram analysis • Flowcharts • Check sheets • Process mapping • Cause/effect diagrams	• Simple techniques that are commonly used to gather and organize data, structure risk management processes and facilitate decision-making	• Compilation of observations, trends or other empirical information to support a variety of less complex deviations, complaints, defaults or other circumstances
Risk ranking and filtering	• Method to compare and rank risks • Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk score	• Prioritizing operating areas or sites for audit or assessment • Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool
Fault-tree analysis	• Method used to identify all root causes of an assumed failure or problem • Used to evaluate system or subsystem failures one at a time, but can combine multiple causes of failure by identifying causal chains • Relies heavily on full process understanding to identify causal factors	• Investigate product complaints • Evaluate deviations

Risk management tool	Description, attributes	Potential applications
Tools		
Hazard operability analysis (HAZOP)	• Tool assumes that risk events are caused by deviations from the design and operating intentions • Uses a systematic technique to help identify potential deviations from normal use or design intentions	• Access manufacturing processes, suppliers, facilities and equipment • Commonly used to evaluate process safety hazards
Hazard analysis and critical control point (HACCP)	• Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring • Bottom-up approach that considers how to prevent hazards from occurring and/or propagating • Emphasizes strength of preventive controls rather than ability to detect	• Better for preventive applications than reactive • Valuable precursor or complement to process validation • Assessment of the efficacy of critical control points and the ability to consistently execute them for any process
Failure modes effects analysis (FMEA)	• Assumes comprehensive understanding of the process and that CPPs have been defined prior to initiating the assessment. Tool ensures that CPPs will be met. • 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	• Evaluate equipment and facilities; analyse a manufacturing process to identify high risk steps and/or critical parameters

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Risk management tool	Description, attributes	Potential applications
Tools		
Failure modes effects analysis (FMEA)	• Highly dependent upon strong understanding of product, process and/or facility under evaluation • Output is a relative "risk score" for each failure mode	

6.1 Preliminary Hazard Analysis (PHA)

This section is based on the ICH Q9(R1) guideline on Quality risk management (2).

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system.

The tool consists of:

- The identification of the possibilities that the risk event happens.
- The qualitative evaluation of the extent of possible injury or damage to health that could result.
- A relative ranking of the hazard using a combination of severity and likelihood of occurrence.
- Identify required hazard controls and follow-up actions.

All hazards and possible accidental events must be identified. It is important to consider all parts of the system, operational modes, maintenance operations, safety systems, and so on. All findings shall be recorded. No hazards are too insignificant to be recorded.

The results of the PHA are usually reported by using a PHA worksheet (or, a computer program).

Example of (PHA worksheet)

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System: Operating mode: Analyst: Date:

Ref.	Hazard	Accidental event (what, where, when)	Probable causes	Contingencies/ Preventive actions	Prob.	Sev.	Comments

6.2 Supporting Statistical Tools

This section is based on the ICH Q9(R1) guideline on Quality risk management (2).

Statistical tools provide a systematic and data-driven approach to risk evaluation, enabling organizations to identify potential risks, quantify their impact, and develop effective mitigation strategies to improve decision-making and enhance overall risk management. Statistical tools offer a quantitative approach to risk evaluation, enabling organizations to analyze data, identify patterns, and make informed decisions. They help organizations analyze historical data, identify patterns, and estimate the likelihood of future events.

Several statistical tools are commonly used in risk assessment to analyze and summarize data .

- graphical tools like histograms, scatter plots, and box plots can be used to visualize and represent risk data
- Regression analysis also allows organizations to assess the statistical significance of the relationship between variables
- Time series analysis involves examining the historical patterns and relationships in the data and using this information to develop forecasting models.
- Control charts.
- Pareto Charts.
- Design of Experiments (DOE)

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- Process Capability Analysis

References and Further Reading

1 Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, 10th ed. Good manufacturing practices and inspection. Geneva, World Health Organization, 2024 ISBN 978-92-4-008608-1 (https://www.who.int/publications/i/item/9789240086081, accessed 29 July 2026).

2 ICH harmonised guideline. ICH Q9(R1): Quality risk management. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, adopted 18 January 2023 (https://www.ich.org/page/quality-guidelines, accessed 29 July 2026).

3 ICH harmonised guideline. ICH Q8(R2): Pharmaceutical development. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, August 2009 (https://www.ich.org/page/quality-guidelines, accessed 29 July 2026).

4 Guidance for industry: PAT — A framework for innovative pharmaceutical development, manufacturing and quality assurance. US Food and Drug Administration, Center for Drug Evaluation and Research (FDA CDER), September 2004 (https://www.fda.gov/media/71012/download, accessed 29 July 2026).

5 ICH harmonised guideline. ICH Q10: Pharmaceutical quality system. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 4 June 2008, section 1.6.1: Knowledge management (https://www.ich.org/page/quality-guidelines, accessed 29 July 2026).

6 Frank T et al. Quality risk management principles and industry case studies, December 2008. Sponsored by the Product Quality Research Institute Manufacturing Technology Committee (PQRI-MTC) (https://pqri.org/wp-content/uploads/2016/03/Quality_Risk_Management_Principles_and_Industry_Case_Studies_December_28_2008.pdf, accessed 29 July 2026).

7 International Organization for Standardization. ISO 31000:2018. Risk management — Guidelines. Geneva, ISO, 2018 (https://www.iso.org/standard/65694.html, accessed 29 July 2026).

8 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Q9(R1) quality risk management training materials. ICH, October 2023 (https://www.ich.org/page/quality-guidelines, accessed 29 July 2026).

9 Boedecker B. GMP Inspectorate of Hannover, Germany. EU GMP requirements – quality systems. Presentation Ankara, Turkey Ministry of Health, 20–21 October 2009.

10 EudraLex. The rules governing medicinal products in the European Union, Vol. 4: Good manufacturing practice (GMP) guidelines. Brussels, European Commission (https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en, accessed 29 July 2026).

11 WHO guideline on the implementation of quality management systems for national regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 13 (https://www.who.int/publications/m/item/trs-1025-annex-13-qms-nra, accessed 29 July 2026).

Draft

12 Guidance on good manufacturing practices: inspection report. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 4 (https://www.who.int/publications/m/item/guidance-on-good-manufacturing-practices-inspection-report, accessed 29 July 2026).

13 Good review practices: guidelines for national and regional regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 9 (https://www.who.int/publications/i/item/9789241209922, accessed 15 September 2026).

14 US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER)/Center for Biologics Evaluation and Research (CBER)/Center for Veterinary Medicine (CVM). Guidance for industry: process validation — general principles and practices (Revision 1). Silver Spring, MD, FDA, January 2011 (https://www.fda.gov/files/drugs/published/Process-Validation--General-Principles-and-Practices.pdf, accessed 29 July 2026).

15 Stamatis DH. Failure mode and effect analysis: FMEA from theory to execution, 2nd ed. Milwaukee, WI, ASQ Quality Press, 2003.

16 Guidelines for failure modes and effects analysis (FMEA) for medical devices. Ontario, Canada, Dyadem Press, 2003 (available via CRC Press/Routledge).

17 Mikulak RJ, McDermott R, Beauregard M. The basics of FMEA, 2nd ed. New York, Productivity Press, 2009.

18 IEC 61882:2016. Hazard and operability studies (HAZOP studies) — application guide, edition 2.0. Geneva, International Electrotechnical Commission, 2016.

19 Application of hazard analysis and critical control point (HACCP) methodology to pharmaceuticals. In: Quality assurance of pharmaceuticals. A compendium of guidelines and related materials.Vol. 2, 2nd updated ed. Good manufacturing practices and inspection. Geneva, World Health Organization, 2007; Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. World Health Organization, 2011 (CD-ROM) (https://iris.who.int/bitstream/handle/10665/43532/9789241547086_eng.pdf?sequence=1&isAllowed=y).

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