



WHO GUIDELINE ON QUALITY RISK MANAGEMENT

This guideline has been prepared by Dr Simon Mills, United Kingdom.

Please address any comments on this proposal, by 1 October 2010 to Dr A.J. van Zyl, Head of Inspections, Prequalification Programme, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: vanzyla@who.int with a copy to gaspardm@who.int.

During the past few years we have moved more towards an electronic system for sending out our working documents for comment, for convenience and in order to speed up the process. If you do not already receive our documents electronically, please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.

© World Health Organization 2010

All rights reserved.

This draft is intended for a restricted audience only, i.e. the individuals and organizations having received this draft. The draft may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means outside these individuals and organizations (including the organizations' concerned staff and member organizations) without the permission of the World Health Organization. The draft should not be displayed on any web site.

Please send any request for permission to:

Dr Sabine Kopp, Quality Assurance Programme, Quality Assurance & Safety: Medicines, Department of Medicines Policy and Standards, World Health Organization, CH-1211 Geneva 27, Switzerland. Fax: (41-22) 791 4730; e-mail: kopps@who.int with a copy to bonnyw@who.int.

The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this draft. However, the printed material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization.

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

First draft points for consideration prepared by Dr Simon Mills, UK	May 2010
Review of initial draft points in informal consultation on quality assurance systems, medicines and risk analysis	4-6 May 2010
Preparation by Dr Mills of more elaborated draft for circulation	August 2010
Circulation for comments	August 2010
Presentation to 45 th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Any further action as necessary	...

CONTENTS

	page
1. INTRODUCTION	4
1.1 Background and scope	4
1.2 Principles of quality risk management (QRM)	5
2. QRM CONSIDERATIONS FOR MEDICINES REGULATORY AUTHORITIES	7
2.1 Assessment of dossiers	7
2.1.1 QRM system	8
2.1.2 Standard operating procedures	8
2.1.3 QRM deficiencies	8
2.2 Inspection activities	8
2.2.1 Inspection of a QRM system	8
2.2.2 Inspection of individual risk-based decisions	9
3. QRM AND PHARMACEUTICAL MANUFACTURERS	10
3.1 Training and education	10
3.2 Responsibilities	10
3.3 Initiating a QRM process	
3.3.1 Assemble a QRM team	11
3.3.2 Define the product and process	11
3.3.3 Identify the intended use of the product	11
3.3.4 Construct and confirm a flow diagram	12
3.4 Risk assessment	12
3.5 Risk control	12
3.6 Risk communication and documentation	13
3.7 Risk control monitoring and review	14
3.8 Establishment of corrective actions	15
3.9 Verification of a QRM plan	15
3.10 Product development	16
3.11 Validation and qualification	17
4. RISK MANAGEMENT TOOLS	18
5. GLOSSARY	21
6. REFERENCES	23
ANNEXES	24

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 provide good assurance that risks are largely controlled. However, in countries where control is less effective, patients may be put at risk through the production of drugs 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.

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 (RM) guidance to the pharmaceutical industry (3). The aim has been to assist the development and implementation of effective RM plans covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing and distribution. HACCP is science-based and systematic and identifies specific hazards and measures for their control, as well as providing information on environmental protection and labour safety. HACCP is a tool to assess hazards and establish control systems that focus on prevention rather than relying on corrective action based on end-product testing. All HACCP systems are capable of accommodating changes, such as advances in equipment design and processing procedures or technological developments.

However, recent 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 RM 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.

International medicines regulatory authorities (MRAs) are encouraging pharmaceutical manufacturers to adopt a risk-based approach to the development of drug products. 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 and MRAs
 - MRAs: systematic and structured planning of reviews and inspections. The submission review and inspection programmes can also operate in a coordinated and synergistic manner.
 - Manufacturers: development, manufacture, distribution of medicines. RM can be an integral element of organizational culture.
- b) Science-based decision-making can be embedded into practice
 - MRAs: company decisions easier to scrutinize. Acceptance of residual risks through understanding the RM decisions involved.
 - Manufacturers: quality decisions and filing commitments can be based on science-based process understanding and RM (quality by design). Process control focused on critical attributes. Uncertainty can be addressed explicitly.

- c) Resources can be focused on risks to patients
- MRAs: RM 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. Supports a corporate culture to 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 process understanding. Improvement and innovation by manufacturers is 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. Real-time batch release is feasible. Innovation and the adoption of latest scientific advances in manufacturing and technology are supported.
- e) Communication and transparency are facilitated
- MRAs: facilitated dialogue with pharmaceutical manufacturers and tailoring of the inspection programme. Improved clarity of a company's decision-making process and judgement on critical issues.
 - 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 minimizing 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. QRM should ensure the evaluation of risk to quality based on scientific knowledge and experience that ultimately links to the protection of the patient.

This guideline will align with the general framework described within other current international papers on this subject.

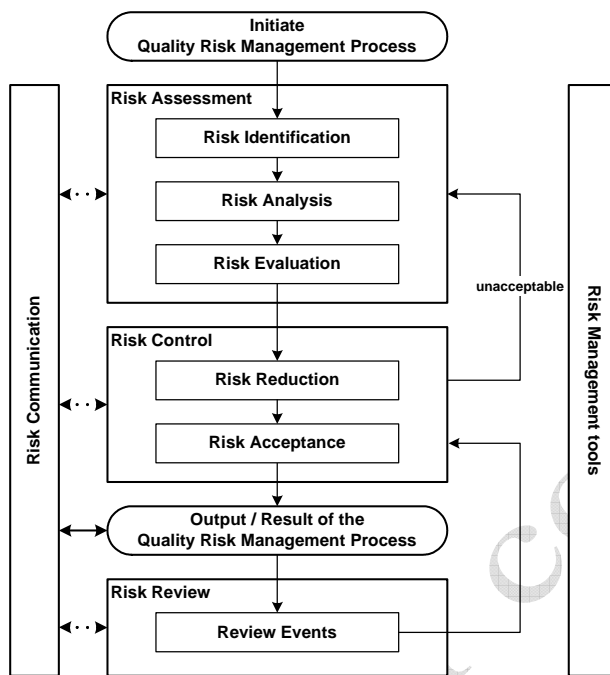
1.2 Principles of quality risk management

Four primary principles of QRM are:

- the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient;
- QRM should be dynamic, iterative and responsive to change;
- the level of effort, formality and documentation of the QRM process should be commensurate with the level of risk; and
- the capability for continual improvement and enhancement should be embedded in the QRM process.

This guidance describes the WHO approach to RM, using the concepts described in ICH Q9 and illustrated in Figure 1 (reproduced from ICH Q9). Other RM models could be used instead. 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



Taken from reference 5: ICH Q9: Quality Risk Management. This figure is also available on the ICH website 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 RM plan;

- facilitate the transfer of process knowledge and product development history to ease product progression and to supplement generic corporate knowledge; and
- enable the pharmaceutical industry to adopt a risk-based approach to development as described in external regulatory guidance (5-8). The RM 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 RM process is to manage risks and knowledge gaps associated with formulation development of the finished pharmaceutical product (FPP) according to the pharmaceutical product target profile (PPTP). In recognizing risks and knowledge gaps, the RM process plays a significant role in proactively enabling the prioritization and mitigation of risks. The objective is to develop the FPP through risk mitigation and the closing of knowledge gaps.

As FPP development progresses, in addition to supporting that development, the purpose of the RM process is to determine and manage risks to bioavailability, safety, efficacy and product quality from processing parameters and attributes. QRM in development should differentiate quality process parameters (QPPs) and quality attributes (QAs) from quality critical process parameters (QCPPs) and critical quality attributes (CQAs), respectively so 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 externally 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 plans are focused on the process of product development, ultimately to ensure a robust and safe FPP. The existence and effectiveness of good clinical practices (GCP), good laboratory practices (GLP) and GMP should also be assessed when drawing up QRM plans.

2. QRM CONSIDERATIONS FOR MEDICINES REGULATORY AUTHORITIES (2,9)

2.1 Assessment of dossiers - 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).

2.1.1 QRM system

All manufacturing authorization holders, developing countries' manufacturing sites and API manufacturers must have a system for QRM. Inspectors will review the QRM system as part of the quality systems section of the inspection (along with complaints, recalls, deviations, product quality reviews, etc.). 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.

2.1.2 Standard operating procedures

The inspected organization must have a standard operating procedure (SOP) integrated with its quality system that defines 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.

2.1.3 QRM deficiencies

As with other areas of inspection, deficiencies will be categorized dependent on the significance of the findings. Typically, the complete lack of a system should be classed as a major deficiency, while lesser deviations within a system would be classed as other. Critical deficiencies may reference QRM where risk assessments have inappropriately supported release of products that pose a threat to patient safety. QRM deficiencies may be grouped with other quality systems deficiencies under a quality systems heading, with factual statements clearly recording what are seen as deficiencies.

2.2 Inspection activities

Inspectors should expect inspected companies to demonstrate that appropriate skill, scientific knowledge, local 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 sub-sections provide inspection guidance in highlighting typical areas for scrutiny.

2.2.1 Inspection of a QRM system (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 quality management system;
- there should be an appropriate number of personnel with relevant qualifications, experience and training. Their responsibilities should be clearly defined;
- senior management should be involved in the identification and implementation of QRM principles within the company;
- the risk management procedures for each area of application should be clearly defined;
- general QA standards should be applied to QRM-related documentation; and

- there should be clear evidence of sufficient resources being available to execute a company's QRM activities.

b) RM procedures:

- the workflow in relation to QRM activities should be systematic and conducted in a logical order. Those relevant to the inspection should be complete;
- there must be a clear overriding impression and evidence that all RM procedures are oriented towards patient safety. The procedures for risk-based decisions and formality of approach should be commensurate with the level of patient risk;
- there should be a logical approach to selection of methods and tools supporting a company's RM 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 must not underrate the likelihood, consequences or 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.

2.2.2 Inspection of individual risk-based decisions (11)

(a) QRM system:

- the documented internal QRM and quality system procedures must be adhered to.

(b) RM activity:

- the risk question/problem should have been clearly defined;
- the people involved in the RM activity should have been suitably qualified and the team in combination should have appropriate expertise to address the question/problem defined;
- all relevant stakeholders should have participated at an appropriate level in the RM procedure;
- there should be a logical approach to selection of methods and tools supporting the risk-based evaluation and a systematic approach applied to prosecution of the RM activities;
- the key risks should have been adequately identified and analysed, with all relevant data having been generated and/or considered. All data reviewed must be from a reliable database. The risk acceptance criteria must 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 reaction time invested in the RM activity should be proportionate to the importance of the identified problem. Critical issues should have been addressed with appropriate high urgency and formality and risk-based decisions made by staff with appropriate 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 RM activities should have been completed in a reasonable time frame and should be accessible to relevant staff and traceable at the time of inspection.

3. QRM AND PHARMACEUTICAL MANUFACTURERS

3.1 Training and education

As QRM is a relatively new concept in the pharmaceutical industry, training of personnel in industry, government and universities in QRM principles and applications is essential for its effective implementation. Industry employees must understand what QRM is, learn the skills necessary to make it function properly, and must also be given the materials and equipment necessary to enable the effective practice of the QRM principles and prosecution of product-specific plans.

In developing the training programme to support a particular QRM plan, working instructions and procedures should be drawn up which clarify the strategy and define the tasks of all involved in the plan. Specific training should be provided as required to enhance awareness. Staff who have responsibility for managing and reviewing risks must 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 control authorities to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of QRM.

The success of a QRM system depends on educating and training management and employees in the importance of their role in producing safe pharmaceuticals. Information should also be provided on the control of hazards at all stages of production and supply.

3.2 Responsibilities

Successful implementation of a QRM plan is dependent on a clear understanding of responsibilities for all staff involved in the plan as it progresses. It is recommended that a cross-functional matrix of assigned responsibilities and accountabilities is drawn up and shared with all relevant personnel. For a more complete picture of the communication pathways, the drafting of a RACI (Responsibility/Accountability/Consulted/Informed) grid should be considered.

The pharmaceutical manufacturer should assure that product-specific knowledge and expertise are available for the development of an effective QRM plan. 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, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) 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 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 qualified person (QP). The extent of involvement and responsibility/accountability must be documented in a technical agreement between the individual and the pharmaceutical company. Regarding QPs, 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 plan is defined, resourced, deployed and reviewed. The leader and team will need to identify critical resources to progress the QRM plan, and also specify a timeline, deliverables and appropriate levels of decision-making for the RM process.

3.3 Initiating a QRM process

A QRM plan should include 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 (3).

3.3.1 Assemble a QRM team

The pharmaceutical manufacturer should assure that product-specific knowledge and expertise are available for the development of an effective QRM plan. This may be best accomplished by assembling a multidisciplinary team according to guidance in section 3.2.

Team members should be able to:

- (a) conduct a hazard analysis;
- (b) identify potential hazards;
- (c) identify hazards which should be controlled;
- (d) recommend controls and critical limits;
- (e) devise procedures for monitoring and verification;
- (f) recommend appropriate corrective action where deviations occur; and
- (g) verify the QRM plan.

The scope of the QRM plan should be defined. The scope should describe the segment of the process involved and the classes of hazards to be addressed should be identified.

3.3.2 Define the product and process

A full description of the product and the process should be drawn up, including relevant quality information such as the composition, physical/chemical properties, structure, pH, temperatures, method of cleaning, bactericidal/ bacteriostatic treatments (e.g. heat-treatment), drying, screening, mixing, blending, packaging and the storage conditions. The method of distribution and transport should also be described, especially where products are thermolabile.

3.3.3 Identify the intended use of the product

The intended use of the product (API and/or FPP) should be based on the expected uses of the product by the end-user or consumer. In specific cases, vulnerable population groups, e.g. geriatric patients, infants and immunocompromised patients, may have to be considered.

3.3.4 Construct and confirm a flow diagram

A flow diagram should be constructed by the QRM team, covering all operations and decisions in the process under development. 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. The QRM team should then confirm the processing operation against the flow diagram during all stages and hours of operation. Amendments to the flow diagram may be made where appropriate, and should be documented.

3.4 Risk assessment (3)

When hazard identification and risk analysis is conducted safety concerns must be distinguished from quality concerns.

The QRM team should list all the hazards that may be reasonably expected to occur at each step from production, testing and distribution up to the point of use. It should then conduct a hazard analysis to identify for the QRM plan which hazards 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 control point. A two-stage risk analysis is recommended. During the first stage, the team should review the materials, activities, equipment, storage, distribution and intended use of the product. A list of the potential hazards (biological, chemical and physical) which may be introduced, increased or controlled in each step should be drawn up. In the subsequent risk analysis the following basic questions should be addressed:

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

The QRM team should then decide which potential hazards should be addressed in the QRM plan and what control measures, if any, exist that can be applied for each hazard. If a hazard has been identified at a step where control is necessary for safety, and no control measure exists at that step or 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 hazard and more than one hazard may be controlled by a specified control measure.

This activity 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 RM tools is discussed further in section 4 of this guidance.

Potential hazards in relation to at least 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; and
- risk of explosions.

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 4). 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.

The expectation of QRM is to assess risks to the medicinal product and patient and then manage both 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. If this can be achieved in a more cost-effective manner whilst maintaining or reducing risk to the product and patient then this is acceptable (9). Inappropriate risk assessment and mitigation in order to achieve cost savings but which could be to the detriment of the patient must be avoided.

3.5 Risk control

Risk assessments should be controlled within a defined document management system.

Acceptance limits must be specified and verified, if possible, for each critical risk requiring control. More than one acceptance limit may sometimes be elaborated at a particular step. The criteria used often include measurements of temperature, time, moisture level, pH and sensory parameters, such as visual appearance and texture. Acceptance limits should be based upon scientific knowledge of the process.

If risk assessments are conducted to justify controls for an ongoing process then the assessments should be subject to change control and periodic review, e.g. line clearance risk assessment. Frequency of review should be appropriate for the nature of the process. Such risk assessments should be seen as living documents that are visible and subject to change as required.

Risk assessments that were conducted as one-off activities to assess a situation that will not recur need not be controlled in a “live” manner but must be documented, approved and retained, e.g. assessment of storage temperature excursion. Such one-off activities should be controlled as live documents if any conclusions are to be used in any future relevant situations, e.g. another storage temperature excursion. Ultimately these may then need to be reviewed in light of experience or developments.

3.6 Risk communication and documentation

Communication of the QRM process must include all 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, the QRM team will ensure buy-in and support. The output of the QRM process and associated risk analysis justifying the approach should be documented and endorsed by the organization's quality unit. Additionally, this information should be communicated to stakeholders for their information and to ensure their support.

It is not necessary to issue a full report for every risk assessment; the level of effort, formality and documentation of the QRM process can be commensurate with the level of risk (2). An organization can be pragmatic regarding the degree of formality that is required; however, appropriate evidence of mitigating activities should be available and a written output must be retained. Increased formality and detail will be expected for more significant risk.

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, consequences or detection of occurrences such that the patient risk is underestimated. The factual evidence behind statements must be robust to challenge by MRA inspectors.

All key risks within an organization should be listed in a register document for the purposes of inspection. This risk register (or equivalent title document) 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 included in or linked to the register. A management process should be in place to review RM – this may be incorporated into the quality management review process.

3.7 Risk control monitoring and 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.

The monitoring procedures used must be able to detect loss of control and this information should ideally be available in time to make adjustments to ensure control of the process and prevent violations of the acceptance limits. Where possible, process adjustments should be made when the monitoring results indicate a trend towards loss of control. These adjustments should be made before a deviation occurs.

Data derived from monitoring must be evaluated by a designated person with the knowledge and authority to carry out corrective actions when indicated.

If monitoring is not continuous, the amount or frequency of monitoring must be sufficient to guarantee that the risk is under control.

Most monitoring procedures for risk control measures will need to be done rapidly because they relate to online processes and there will not be time for lengthy analytical testing. For this reason physical and chemical measurements are often preferred to microbiological tests because they can be done rapidly and can often indicate the microbiological control of the product.

The personnel conducting the monitoring of risks and their control measures should be engaged in production (e.g. line supervisors, maintenance staff) and, where appropriate, QC staff. They should be trained in monitoring procedures.

Where continuous monitoring is possible a reliable monitoring procedure and frequency should be identified. Statistically designed data collection or sampling systems should then be used.

All records and documents associated with monitoring risks and their control measures must be signed and dated by the person(s) carrying out the monitoring and by a responsible reviewing official(s) of the company.

3.8 Establishment of corrective actions

Specific corrective actions should be developed for each risk in the QRM system in order to deal with deviations when they occur. These actions should ensure that the risk is brought under control. Corrective actions should include at least the following:

- (a) determination and correction of the cause of non-compliance;
- (b) determination of the disposition of the non-compliant product; and
- (c) recording of the corrective actions that have been taken.

Specific corrective actions should be developed in advance for each identified risk and included in the QRM plan. As a minimum this plan should specify 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. Individuals who have a thorough understanding of the process, product and QRM plan should be assigned the responsibility for the oversight of corrective actions.

As appropriate, experts may be consulted to review the information available and to assist in determining the disposition of non-compliant product. Actions taken must also include the proper disposition of the affected product.

Deviation and product disposition procedures must be documented in the QRM records.

3.9 Verification of a QRM plan (3)

The QRM plan that is put in place needs to be verified. Verification and auditing methods, procedures and tests, including random sampling and analysis, can be used to determine whether the QRM system is working correctly. The frequency of verification should be sufficient to confirm the proper functioning of the QRM system.

Examples of verification activities include:

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

Initial verification of the QRM plan is necessary to determine whether it is scientifically and technically sound, that all hazards have been identified and that, if the QRM plan is properly implemented, these hazards will be effectively controlled.

Information reviewed to verify the QRM plan 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 hazards are recognized. Where possible verification should include actions to confirm the efficacy of all elements of the QRM plan.

In addition, a periodic comprehensive evaluation of the QRM system by an unbiased, independent third party is useful. This should include a technical evaluation of the hazard analysis and each element of the QRM plan as well as an on-site review of all flow diagrams and appropriate records of the operation of the plan. Such a comprehensive verification is independent of other verification procedures and must be performed in order to ensure that the QRM plan is resulting in the control of the hazards. If the results of the comprehensive verification identify deficiencies, the QRM team should modify the QRM plan as necessary.

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

3.10 Product development

The application of RM 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 PPTP. The first RM exercise should be performed once the PPTP 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 RM 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.

3.11 Validation and qualification

In keeping with the principles of QRM and risk-based pharmaceutical development, 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. The current FDA draft process validation guidance reflects this approach (12). A European-based critique of the FDA guidance has also been issued (13).

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 unneeded batches. Clearly, for all decisions of this nature regarding conformance batches, it will be very important to have an effective company/MRA dialogue to agree on requirements for a regulatory submission.

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.

4. 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). As an element of the WHO guidance on QRM, this PQRI report is recommended as a training resource and to gain an understanding into how best to use RM tools.

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), so that a grid or matrix can be constructed.

Table 1. Probability versus impact matrix

	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

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 by the QRM team 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

Score	Probability	Example	Score	Impact	Consequence
1	Rare	<ul style="list-style-type: none"> Seen every 10-30 years 	1	Negligible	<ul style="list-style-type: none"> No regulatory issue No effect on and not noticeable by patient
2	Unlikely	<ul style="list-style-type: none"> Seen every 5-10 years 	2	Marginal	<ul style="list-style-type: none"> May require MRA notification Decision to release product not compromised
3	Possible	<ul style="list-style-type: none"> Seen every 1-5 years 	3	Moderate	<ul style="list-style-type: none"> MRA inspection may identify a major concern but deficiency quite easily resolved Limited product recall possible
4	Likely	<ul style="list-style-type: none"> Seen to occur more than once a year 	4	Critical	<ul style="list-style-type: none"> MRA inspection may conclude serious non-compliance Likely product recall from one or more markets
5	Almost certain	<ul style="list-style-type: none"> Seen several times a year 	5	Catastrophic	<ul style="list-style-type: none"> 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 customised by a QRM team 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 RM tool options available for the purposes of this guideline, the following table has been taken from the PQRI-MTC report¹⁰. The list is not comprehensive but it does include some of the more frequently used approaches.

Table 3. Common risk management tools (10)

Risk management tool	Description/attributes	Potential applications
Basic tools		
Diagram analysis <ul style="list-style-type: none"> • Flowcharts • Check sheets • Process mapping • Cause/effect diagrams 	<ul style="list-style-type: none"> • Simple techniques that are commonly used to gather and organise data, structure RM processes and facilitate decision making 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Method to compare and rank risks • Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk scores 	<ul style="list-style-type: none"> • Prioritize operating areas or sites for audit/assessment • Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool
Advanced tools		
Fault tree analysis (FTA)	<ul style="list-style-type: none"> • Method used to identify all root causes of an assumed failure or problem • Used to evaluate system or sub-system 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 	<ul style="list-style-type: none"> • Investigate product complaints • Evaluate deviations
Hazard operability analysis (HAZOP)	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Access manufacturing processes, facilities and equipment • Commonly used to evaluate process safety hazards
Hazards analysis and critical control points (HACCP)	<ul style="list-style-type: none"> • 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 • Emphasises strength of preventative controls rather than ability to detect • 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. 	<ul style="list-style-type: none"> • Better for preventative applications rather than reactive • Great precursor or complement to process validation • Assessment of the efficacy of CPPs and the ability to consistently execute them for any process <p><i>(continued)</i></p>

Risk management tool	Description/attributes	Potential applications
Advanced tools		
Failure modes effects analysis (FMEA)	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Evaluate equipment and facilities; analyse a manufacturing process to identify high risk steps and/or critical parameters

[Note from the Secretariat: the authors will be contacted regarding copyright of this table.]

Another general overview of and references for some of the risk tools that might be brought to bear in QRM by industry and regulators is provided in Annex 20 (Annex I) of the EU GMP guideline (2).

5. 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”.

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.

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

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.

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 organisation 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 risk management plan.

6. REFERENCES

1. WHO good manufacturing practices: main principles for pharmaceutical products. In: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Second updated edition. Good manufacturing practices and inspection.* Geneva, World Health Organization, 2007.
2. EudraLex - Volume 4, Good manufacturing practice (GMP) Guidelines
http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm.
3. Application of hazard analysis and critical control point (HACCP) methodology to pharmaceuticals. In: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Second updated edition. Good manufacturing practices and inspection.* Geneva, World Health Organization, 2007.
4. FDA News – GMPs for the 21st Century; M Anisfeld; Industrial Pharmacy, Dec 2004, I4, P20.
5. ICH Harmonised Tripartite Guideline. ICH Q8: Pharmaceutical Development. May 2006 <http://www.ich.org>.
6. ICH Harmonised Tripartite Guideline. ICH Q9: Quality Risk Management June 2006 <http://www.ich.org>.
7. Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance. FDA (CDER), September 2004 <http://www.fda.gov/Drugs/default.htm>.
8. Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach. FDA (CDER), September 2004 <http://www.fda.gov/Drugs/default.htm>.
9. MHRA Guidance: GMP-QRM – Frequently asked questions
<http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/FAQ/QualityRiskManagement/index.htm>.
10. Quality Risk Management Principles and Industry case Studies; T. Frank et al (Dec 2008); sponsored by the Pharmaceutical Quality Research Institute Manufacturing Technology Committee (PQRI-MTC).
11. EU GMP Requirements – Quality Systems; B Boedecker, Germany; Presentation 20-21 Oct 2009, Ankara, Turkey Ministry of Health.
12. Guidance for Industry – Process Validation: General Principles and Practices; Nov 2008
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>.
13. FDA's New Process Validation Guidance – A detailed analysis; European Compliance Academy, Nov 2008 http://www.gmp-compliance.org/eca_news_1402_5699,6013.html.

ANNEXES

(Examples of QRM application to be added)

[Note from the Secretariat: contributions with examples would be much appreciated.]

Draft for comment