ANNEX 8: QUALITY RISK MANAGEMENT (QRM)

1. INTRODUCTION

1.1 Background and scope

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

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

Since then international guidance has emerged *(2, 4-8)* that is of specific relevance to the pharmaceutical industry and which addresses the full scope of pharmaceutical industry QRM more effectively than HACCP principles, including how to structure regulatory filings using a risk-based approach. Consequently, this WHO guideline has been developed as an update of WHO advice to the pharmaceutical industry, taking account of this new guidance.

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

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

In return for using this approach, there are potential opportunities for both MRAs and pharmaceutical manufacturers *(9)* as summarized in the following sections.

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

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

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

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

- MRAs: decisions regarding review, inspection or inspection frequency should consider product risk and GMP compliance of the manufacturer. The MRA accepts residual risks through understanding the QRM decisions involved.

- Manufacturers: quality decisions and filing commitments can be based on science-based process understanding and QRM (when utilizing the quality by design approach). Its effective application should offer manufacturers greater freedom on how to meet principles of GMP, and this, therefore, should encourage innovation.
  The control strategy for the process focuses on critical quality attributes and critical process parameters. Uncertainty can be addressed explicitly.

c) Resources can be focused on risks to patients:

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

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

d) Restrictive and unnecessary practices can be avoided:

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

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

e) Communication and transparency are facilitated:

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

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

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

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

1.2 Principles of quality risk management

The two primary principles of QRM are:

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

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

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

This guidance describes the WHO approach to QRM, using the concepts described in ICH Q9 and illustrated in Figure 1 (reproduced from ICH Q9). The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

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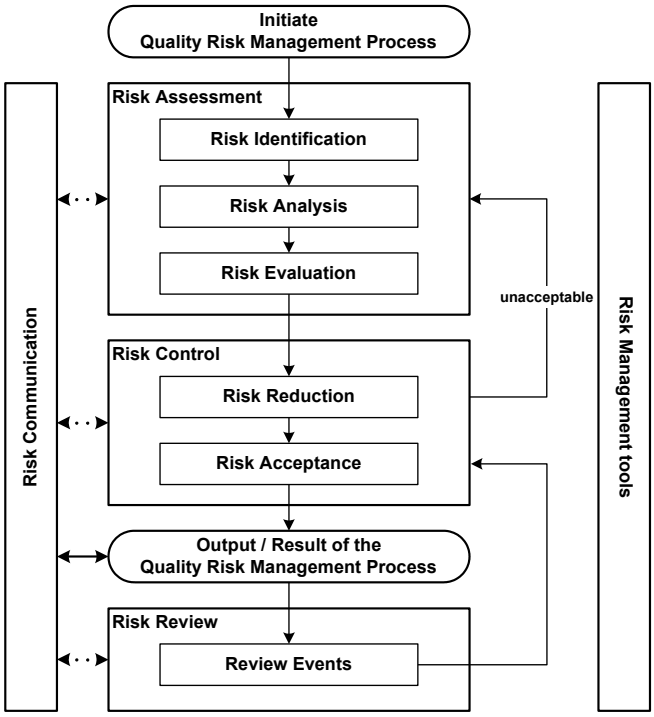
Figure 1. Overview of a typical quality risk management process



Taken from reference 6: 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:

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- systematically analyze products and processes to ensure the best scientific rationale is in place to improve the probability of success;

- identify important knowledge gaps associated with processes that need to be understood to properly identify risks;

- provide a communication process that will best interface with all relevant parties involved in the QRM activities;

- facilitate the transfer of process knowledge and product development history to ease product progression along the life-cycle and to supplement already available knowledge about the product;

- enable the pharmaceutical industry to adopt a risk-based approach to development as described in external regulatory guidance *(4-7)*. The QRM outputs will potentially serve as reference documents to support product development and control strategy discussions in regulatory filings.

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

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

The long process of product development is inevitably complex and requires the continual exchange of data, decisions and updates both internally within companies and, where required with external stakeholders, such as MRAs. A very important aspect of product development and QRM is the maintenance of an effective and secure knowledge management and documentation system. Such a system must facilitate transparent communication and the highlighting of key issues to stakeholders and also

possess a well-structured archive. Clearly, the ability to organize diverse data and information effectively and then retrieve it as required for updating and further evaluation, for the purposes of process validation as an example, would be hugely beneficial.

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

2. QRM PROCESS

2.1 Initiating a QRM process

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

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

2.2 Personnel involved in QRM

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

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The personnel should be able to:

(a) conduct a risk analysis;
(b) identify and analyse potential risks;
(c) identify, evaluate risks and determine which ones should be controlled and which ones can be accepted;

(d) recommend and implement adequate risk control measures;
(e) devise procedures for risk review, monitoring and verification.

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

2.3 Knowledge of the product and process

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

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

2.4 Risk assessment

When risk assessment is conducted safety and efficacy need to be considered in addition to the quality concerns.

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

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

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

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

Options for risk assessment methodologies are described in section 5.

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

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

– materials and ingredients;
– physical characteristics and composition of the product;
– processing procedures;
– microbial limits, where applicable;
– premises;
– equipment;
– packaging;

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– sanitation and hygiene;
– 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 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 judgment should be used in interpretation of factual evidence but must be subject to justification.

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

The expectation of QRM is to assess risks to the product quality and to the patient and then manage these risks to an acceptable level. It is appropriate for companies to assess their control systems to implement the optimum controls to ensure product quality and patient safety. Risk assessment and mitigation in order to achieve cost savings but which could be to the detriment of the patient is an unacceptable practice *(10)*.

2.5 Risk control

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

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

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

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

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

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

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

2.6 Risk review

Appropriate systems should be in place to ensure that the output of the QRM process is periodically monitored and reviewed, as appropriate, to assess new information that may impact on the original QRM decision. Examples of such changes include changes to control systems, changes to equipment and processes, changes in suppliers or contractors and organizational restructuring.

Monitoring is the scheduled measurement or observation of a specific risk control measure relative to its acceptance limits. Monitoring should be recorded.

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

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2.7 Verification of QRM process and methodologies

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

Verification activities include:

(a) review of the QRM process and its records;

(b) review of deviations and product dispositions;

(c) confirmation that identified risks is kept under control.

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

Information reviewed to verify the QRM process should include:

(a) expert advice and scientific studies;

(b) in-plant observations, measurements and evaluations.

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

In addition, a comprehensive review of the QRM process and specific instances of QRM application by an independent third party may be useful. This would include a technical evaluation of the risk analysis and each element of the QRM process and its application as well as an on-site review of all flow diagrams and appropriate records of the

operation of the QRM activity. Such a comprehensive verification is independent of other verification procedures and should be performed in order to ensure that the QRM process is resulting in the control of the risks. If the results of the comprehensive verification identify deficiencies the QRM process should be modified as necessary.

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

2.8 Risk communication and documentation

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

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

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

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

3. QRM APPLICATION FOR PHARMACEUTICALS

3.1 Training and education

Training of relevant personnel in industry, MRAs and universities in QRM principles and applications is essential for its effective implementation. Industry employees should understand what QRM is, possess the skills necessary to apply it properly, and be appropriately resourced to enable the effective practice of the QRM principles.

In developing the training programme to support QRM activities, working instructions and procedures should be drawn up which clarify the strategy and define the tasks of all involved in these activities. Specific training should be provided as required to enhance awareness. Staff which has responsibility for managing and reviewing risks should receive formal training in the relevant procedures.

Cooperation between producers, traders and responsible authorities is of vital importance. Opportunities should be provided for the joint training of industrial staff and MRAs to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of QRM.

The success of QRM depends on educating and training of management and employees in the importance of QRM in producing and supplying safe pharmaceuticals.

3.2 Responsibilities

Successful application of QRM is dependent on a clear understanding of responsibilities for all staff involved in the QRM activities. It is recommended that a cross-functional matrix of assigned responsibilities and accountabilities is drawn up and shared with all relevant personnel.

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For example, one may consider the use of techniques such as RACI (responsibility/accountability/consulted/informed) grids to illustrate a more complete picture of the communication pathways.

The pharmaceutical manufacturer should assure that appropriate knowledge and expertise are available for the effective planning and completion of QRM activities. QRM activities are usually, but not always, undertaken by a matrix of interdisciplinary teams. When teams are formed they should include experts from the appropriate areas (e.g. quality unit, product development, engineering, regulatory affairs, production operations, statistics, clinical and others, such as sales, marketing or legal, as applicable), in addition to individuals who are knowledgeable about the QRM process.

In this respect it is acceptable for external consultants to participate in the QRM matrix team where they can provide specific expertise or knowledge. Their role should be justifiable and clearly defined and resultant accountability must be understood. A technical agreement or other equivalent document with the consultant may be appropriate where a GMP responsibility is assumed.

Similarly, contract staff may become involved to lead or participate in risk assessments, e.g. a contract authorized person. The extent of involvement and responsibility/accountability must be documented in a technical agreement or other equivalent document between the individual and the pharmaceutical company. Regarding the authorized person it is important that a company's internal procedures are clear on where the responsibility lies for final approval of risk acceptance documents.

Effective matrix team leadership is required to take responsibility for coordinating QRM across various functions and departments of their organization and ensuring that the QRM activities are adequately defined, planned, resourced, deployed and reviewed. The leader and team will need to identify critical resources to progress the QRM activities, and also specify a timeline, deliverables and appropriate levels of decision-making for the QRM process.

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3.3 QRM application during product development

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

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

As the product progresses to later stage development, a more detailed analysis of the risks associated with both the API and FPP becomes a requirement. Risks would cover concerns associated with stability, bioavailability and patient safety including any challenges to these resulting from the manufacturing process (including, for example, API form conversion under certain conditions of processing).

As product knowledge advances more detailed QRM exercises can be considered, concentrating on areas considered to be higher priority risk. As the product's critical quality attributes (CQAs) become defined, the potential risks arising from each input material (API, excipients, any device or pack components) and each secondary product unit operation can be investigated.

Eventually, for the developed FPP the increasingly comprehensive risk assessment will support a thorough understanding of the product and will enable all key variables to be identified, understood and controlled.

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3.4 QRM application during validation and qualification

In keeping with the principles of QRM, this guideline recommends that process validation embraces the product life cycle concept already mentioned. Accordingly, process validation activities should involve the generation and evaluation of data throughout the development process into full-scale production that will provide a science-based assurance of consistent delivery of quality product in the production operation *(10, 11, 12)*.

An important emphasis is that the building of scientific assurance begins early in development. It is obtained through rational design of experiments and robust evaluation of data during product/process development through to the commercial production phase at which time the API and drug product CQAs are well understood and controlled. In this scenario, validation or (perhaps more appropriately termed) conformance batches just serve to reinforce the science- or risk-based decisions that have been made as product development has advanced and should demonstrate good control of all identified critical sources of variability. Any unplanned variations within a batch or between batches should be evaluated accordingly, employing suitable statistical tools, e.g. trend analysis, to check on process control.

A potential advantage of this approach is that there can be flexibility in the number of validation or conformance batches required for regulatory scrutiny prior to approval. The traditional number of batches required for validation has been three but, with QRM embedded in a product's development process, the number of conformance batches that needs to be made depends on the depth of knowledge about the process. For very low-volume products, e.g. orphan drugs, this may preclude the need to manufacture multiple batches. It would be beneficial for decisions of this nature regarding conformance batches to have an effective company/MRA dialogue to agree on requirements for a regulatory submission. Until new approaches to demonstrate validation mature and become widely used, the traditional three-batch approach to validate a process is still acceptable.

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

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

3.5 QRM application during commercial manufacturing

QRM principles applied as a process supports science-based and practical decisions when integrated into commercial manufacturing. In general implementing QRM should not obviate a manufacturer's obligation to comply with regulatory expectations (e.g. regulatory requirements, regulatory filings, inspection commitments, etc.). All QRM activities should be structured in a way that allows escalation of risks to the appropriate management level within the organization. Special focus can be on the risk assessment and risk control of, e.g.:

- product quality risks;
- adverse impact to patient health based on product quality defects;
- product supply interruption 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 must be summarized and 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, quality unit, etc.).

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A risk review is important if new risks or changes to existing risk levels are identified through planned or unplanned events such as routine operation, changes, complaints, product returns, discrepancies/deviations, data monitoring, trends, inspections/audits, changes in regulatory environment, etc. Risk review may also include evaluation of, e.g.:

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

In principal there are two focuses when implementing QRM in commercial manufacturing: a system focus and a product focus.

3.5.1 QRM integration with key quality system elements

Effective QRM can facilitate the “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. Situations in which the use of the QRM process might provide information are beneficial in a variety of operations, e.g.:

- integrated quality management: documentation; training and education; quality defects; auditing/inspection; change management/change control (includes equipment, facilities, utilities, control and IT systems); continual improvement/corrective and preventive actions (CAPA);
- facilities, equipment and utilities: e.g. design; qualification; maintenance and decommissioning of facility/equipment; hygiene aspects; cleaning of equipment and environmental control; calibration/preventive maintenance; computer systems and computer-controlled equipment;
- supplier, materials and contract service management: e.g. assessment and evaluation of suppliers and contract manufacturers; starting material; use of materials; storage; logistics and distribution conditions;
- technology transfer: e.g. from development to manufacturing; during commercial manufacturing between sites; from commercial manufacturing to product discontinuation.

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3.5.2 QRM application in product manufacturing operations

Effective QRM can facilitate the "How to do?" and, therefore, ensure products will meet acceptable standards for safety, quality, and compliance.

QRM methodology can support, beside others, the following events to assess and control quality risks, e.g.:

- production: e.g. manufacturing process risks; validation; in-process sampling and testing controls; production planning; deviation and investigation management; change management;
- laboratory control and stability studies: e.g. out-of-specification results; retest period/expiration date; method transfers;
- packaging and labelling: e.g. design of packages; selection of container-closure system; label controls;
- storage, transport and distribution: e.g. cold chain.

4. QRM CONSIDERATIONS FOR MEDICINES REGULATORY AUTHORITIES

(2, 9)

4.1 Introduction

A key principle of this guideline is that all MRAs, developing country manufacturing sites and API manufacturers should demonstrate, wherever appropriate, application of QRM throughout the product life-cycle for development and manufacturing facilities. Inspectors will review this QRM system as part of the quality systems section of the inspection (along with complaints, recalls, deviations, product quality reviews, etc.).

Equally, it is recommended that QRM be applied by the MRAs themselves (reviewers and inspectorates) as there are clear benefits of a QRM-based review and inspection plan. For example, inspectors can allocate time and resource commensurate with their perceived significance of risk in any given situation and can be pragmatic regarding the level of scrutiny and degree of formality required.

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4.2 QRM application to inspection strategy

4.2.1 Risk management in inspections

The inspection section or unit of a medicines regulatory authority should operate within a written, implemented quality management system *(13).* Standard operating procedures (SOPs) should be followed for activities including (but not limited to) inspection planning, review of corrective and preventive actions after inspections and complaint handling and investigation. Where appropriate, the procedures and activities during inspection should be in line with the principles of QRM.

The unit should have a risk management plan (RMP) that describes the philosophy, approach, procedures and implementation of risk management. The risk management plan should be reviewed and updated on a rolling basis, or at least annually and should cover all types of inspections (including GMP, GCP, 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 in a risk assessment worksheet. Records should be maintained.

A metric system should be used for risk ratings, e.g. on a scale from 1 to 3.

4.2.2 Inspection planning and conduct

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

Risk rating should normally be done only for sites that had been previously inspected. The risk assessment worksheet should be completed after every inspection. Inspection of a site that had not been inspected previously may be waived only in cases where a recognition procedure exists between regulatory inspection units, and where in addition appropriate evidence of GXP compliance is available that indicates that there is no or acceptable low risk to products and patients.

Various factors should be considered in the risk assessment exercise, and may be different for the different types of GXP inspections. Risk factors to be considered depend on the type of inspection, and may include:

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(a) outcome of inspection by another regulatory authority;
(b) outcome of the previous inspection;
(c) complexity of the site (e.g. buildings, utilities);
(d) complexity of the product(e.g. sterile, non-sterile);
(e) type of product (e.g. biological, low dose);
(f) complaints and recalls;
(g) significance of changes (e.g. equipment, key personnel);
(h) results of product testing;
(i) risk to the patient;
(j) complex route of synthesis (API);
(k) polymorphism (API);
(l) biopharmaceutical classification of the product;

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. Departures from GXP should be classified where appropriate, as “critical, major or minor”.

The unit should have an SOP that describes the classification process. Classification should be based on risk assessment. The level of risk assigned should be in relation to the nature of the observation as well as the number of occurrences.

4.2.3 Corrective action and preventive action review, and scheduling of routine inspections

Corrective actions and preventive actions (CAPA) should be requested from a site, following an inspection. The CAPAs should address the observations included in an inspection report.

Based on the inspection outcome and the acceptability of the CAPA, the risk rating of the site should be reviewed and recorded.

Inspection frequency should be defined based on the risk rating. For example, a frequency can be defined as every 6, 12, 18 or 24 months. *(The maximum time interval should be no more than every 36 months.)*

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4.2.4 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.

4.3 Inspection of QRM at a manufacturing site

Note. During inspections, inspectors should assess whether a manufacturer has appropriate skills, scientific knowledge as well as product and process knowledge for the QRM procedure being inspected. This is also relevant where a company has made use of contracted parties.

The company's QRM procedure should be appropriately detailed and should be integrated into the company's quality management system. It should cover at least the following areas:

(a) general approach to both planned and unplanned risk assessment – and include scope, responsibilities, controls, approvals, management systems, applicability and exclusions;
(b) personnel with appropriate qualifications, experience and training. Their responsibilities with regard to QRM should be clearly defined;
(c) senior management should be involved in the identification and implementation of QRM principles within the company;
(d) the risk management procedure(s) for each area of application should be clearly defined;
(e) quality assurance principles should be applied to QRM-related documentation, e.g. review, approval, implementation and archiving.

QRM policies and procedures should be clear and the workflow should be systematic and conducted in a logical order.

The procedure for risk management should be implemented. Manufacturers should identify significant risks and consider all the relevant data from reliable sources.

Personnel should be trained and assessed in the principles of QRM.

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Where appropriate, a team of members of personnel should participate in the QRM processes.

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 efficiency 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 in a reasonable time frame and should be accessible.

Risk assessments performed should be reviewed when appropriate, and additional controls implemented when required.

4.4 QRM applied to dossier review (assessment)

NMRA assessment processes 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 best effect, and ultimately ensures that important products are 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 for a given dossier or dosage form, and allocation of resources to the various sections of a dossier for a given product. In addition, product-related risk factors must be managed throughout the lifecycle of the product, for example through effective communication between

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assessors and inspectors, and by establishing systems for dealing with the products after approval.

The prioritization of dossiers should consider the therapeutic needs of the regional population (disease occurrence, the need for paediatric formulations, combination products, etc.) and the availability of medicines on the market. Prioritization should be a dynamic process in order 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 twice or thrice daily dosing products, second-line versus first-line products, flexible dosage forms such as dispersible tablets and variable dose products such as oral liquids.

The screening process examines the completeness of a dossier. Screening ensures that only those dossiers that meet minimum standards for completeness are entered into the full assessment process. Insufficient screening processes allow a lower standard of quality of dossiers to be accepted for review, significantly increasing assessment time.

Identification of dossier related and product related risk factors allows for the allocation of proper 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 semi-synthetic and fermentation products, complex routes of synthesis, polymorphism, isomerism and potential genotoxic impurities, and product related considerations such as the use of novel excipients, the complexity of the formulation, single-ingredient versus fixed-dose combinations, and special delivery systems (modified release, transdermal products, inhalation products, etc.). Once risk factors are identified, resources should be allocated to minimize risk, for example assessors with expertise related to the identified product-related risk should be assigned to assess the dossier whenever possible. When resources allow, organization of assessors may be done according to specialization, assigning assessors into various product categories (e.g. generic products, sterile products, solid oral dosage forms, special delivery systems, etc.). This can facilitate the development of expertise in key areas and promote consistency of review, as well as ensuring that products requiring specialized knowledge are identified and directed to the

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appropriate expertise. Where a high level of risk is identified for a dossier, assignment of more experienced assessors is required, at minimum on a consultative 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 increased risk that the overall product quality may be poor.

Allocation of resources to various aspects/sections of the dossier is an important QRM consideration, in order to ensure that the resources used are commensurate to the associated 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 time in the assessment process. Examples include the clinical/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 for most simple solid oral products is that more time should be allocated to the review of manufacturing steps prior to packaging, compared to the time allotted to review the packaging process.

During the assessment process there should be a standard procedure to communicate to inspectors those identified issues 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. A clear guideline that outlines possible post-approval changes and assigns an associated risk level is an effective means to achieve this.

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5. RISK MANAGEMENT TOOLS

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

The Product Quality Research Institute (PQRI) Manufacturing Technology Committee (MTC) has produced a summary *(10)* of common RM principles and best practices, several working tools to foster consistency in the use of ICH Q9 *(6)* in day-to-day RM decision-making, and a series of examples of RM applications currently in use by major pharmaceutical firms. They have also produced very helpful risk tool training modules for risk ranking and filtering, failure modes effects analysis (FMEA) *(14, 15, 16)*, hazard operability analysis (HAZOP) *(17)* and HACCP *(3)*

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

Table 1. An example of a probability versus impact matrix

	Impact				
Probability	Negligible	Marginal	Moderate	Critical	Catastrophic
Almost certai	5	10	15	20	25
Likely	4	8	12	16	20
Possible	3	6	9	12	15

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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 in the QRM process after consideration of the specific consequences for the process undergoing risk assessment. These consequences can be split according to the probability and impact scores, as exemplified in Table 2.

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

Score	Probability	Example
1	Rare	• Seen every 10-30 years
2	Unlikely	• Seen every 5-10 years
3	Possible	• Seen every 1-5 years
4	Likely	• Seen to occur more than

Score	Impact	Consequence
1	Negligible	• No regulatory issue • No effect on and not noticeable by patient
2	Marginal	• May require MRA notification • Decision to release product not compromised
3	Moderate	• MRA inspection may identify a major concern but deficiency quite easily resolved • Limited product recall possible
4	Critical	• MRA inspection may conclude serious non-

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		once a year			compliance • Likely product recall from one or more markets
5	Almost certain	• Seen several times a year	5	Catastrophic	• Enforcement action by MRA such as consent decree, product seizure • Global product recall

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

As a summary of the common, well-recognized QRM tool options available for the purposes of this guideline, the following table has been based on the one from the PQRI-MTC report *(10)*. The list is not comprehensive but it does include some of the more frequently used approaches.

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

Risk management too	**Description/attributes**	**Potential applications**
Basic tools		
Diagram analysis • Flowcharts • Check sheets • Process mapping • Cause/effect diagrams	• Simple techniques that a commonly used to gather ar organize data, structure R processes and facilita decision-making	Compilation of observations, trend or other empirical information to support a variety of less complex deviations, complaints, defaults or other circumstances
Risk ranking and filterir	• Method to compare ar rank risl	Prioritize operating areas or sites for audit/assessment

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Risk management too	Description/attributes	Potential applications
Basic tools		
	• Typically involves evaluation multiple diverse quantitativ and qualitative factors for eac risk, and weighting factors ar risk score	Useful for situations when the risk and underlying consequences are diverse and difficult to compare using a single tool
Advanced tools		
Fault tree analysis (FTA	• Method used to identify all ro causes of an assumed failu or proble • Used to evaluate system subsystem failures one at time, but can combine multip causes of failure b identifying causal chair • Relies heavily on full proces understanding to identi causal factors	Investigate product complaints Evaluate deviations
Hazard operabili analysis (HAZOP)	• Tool assumes that risk even are caused by deviations from th design and operatir intentions • Uses a systematic techniqu to help identify potenti deviations fro normal use or desig intentions	Access manufacturing processes, suppliers, facilities and equipment Commonly used to evaluate process safety hazards
Hazards analysis ar critical control poin	• Identify and impleme process controls that consistent and effectively prevent hazard	Better for preventative application rather than reactive Great precursor or complement to

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Risk management too	Description/attributes	Potential applications
Basic tools		
(HACCP)	conditions from occurrir • Bottom-up approach th considers how to prevent hazards fro occurring and/or propagatir • Emphasizes strength preventative controls rath than ability to detect	process validation Assessment of the efficacy of CPPs and the ability to consistently execute them for any process
Failure modes effec analysis (FMEA)	• 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. • Assesses potential failu modes for processes, and th probable effect on outcome and/or product performanc • Once failure modes a known, risk reduction actior can be applied to eliminate, reduc or control potential failure • Highly dependent upc strong understanding product, process and/ facility under	Evaluate equipment and facilities; analyze a manufacturing process identify high risk steps and/or critical parameters

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Risk management too	Description/attributes	Potential applications
Basic tools		
	evaluation • Output is a relative "ri score" for each failure mode	

[Note from the Secretariat: the authors will be contacted regarding copyright of the above 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)*.

6. GLOSSARY

[Note from the secretariat: Glossary will be double-checked against the most up-to-date definitions in the final version.]

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

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control (ICH Q10).

Critical quality attribute (CQA) (source: ICH Q8)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Finished pharmaceutical product (FPP)

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

Formal experimental design (source: ICH Q8)

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “design of experiments”.

Pharmaceutical product

Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Pharmaceutical product target profile (PPTP)

A definition of the target properties of the FPP, including dosage form and strength(s), route of administration and relevant drug release and pharmacokinetic requirements

Planned risk assessment

An assessment that is conducted in advance of an activity, either before any work is conducted or before further work is conducted. This enables quality to be built into

activities and risk reduced, e.g. design of high containment facilities for manufacture of cytotoxic products.

Process robustness (source: ICH Q8)

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

Product quality research institute (PQRI)

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

Qualification

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

Quality critical process parameter (source: ICH Q8)

A process parameter whose variability has an impact on a critical quality attribute and, therefore, should be monitored or controlled to ensure the process produces the desired quality.

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

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

Validation
The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes-including equipment, buildings, personnel and materials are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do.

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

7. REFERENCES

1. Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, Second updated edition. 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) (http://apps.who.int/medicinedocs/en/q/).

2. EudraLex - Volume 4, Good manufacturing practice (GMP) Guidelines;

   http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm.

ANNEX 8: QUALITY RISK MANAGEMENT (QRM)

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. Vol. 2, Second updated edition. 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) (http://apps.who.int/medicinedocs/en/q/).

4. FDA News – GMPs for the 21st Century; M Anisfeld; Industrial Pharmacy, Dec 2004, I4, P20.

5. ICH Harmonised Tripartite Guideline. ICH Q8(R2): Pharmaceutical Development. August 2008; 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.

ANNEX 8: QUALITY RISK MANAGEMENT (QRM)

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. Frank T et al (December 2008) sponsored by the Pharmaceutical Quality Research Institute Manufacturing Technology Committee (PQRI-MTC).

11. EU GMP Requirements – Quality Systems; Boedecker B, Germany; Presentation 20-21 Oct 2009, Ankara, Turkey Ministry of Health.

12. WHO guidelines on quality system requirements for national GMP inspectorates: http://www.who.int/medicines/areas/quality_safety/quality_assurance/inspections/en/index.html.

13. Guidance for Industry – Process Validation: General Principles and Practices; Nov 2008; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf.

14. Failure Mode and Effect Analysis. FMEA from Theory to Execution. 2nd Edition 2003. D. H. Stamatis, ISBN 0873895983.

15. Guidelines for Failure Modes and Effects Analysis (FMEA) for Medical Devices. 2003 Dyadem Press, ISBN 0849319102.

16. McDermott R et al (1996) The Basics of FMEA. ISBN 0527763209.

17. IEC 61882 - Hazard Operability Analysis (HAZOP).

ANNEX 8: QUALITY RISK MANAGEMENT (QRM)

Further reading

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.

Validation of analytical procedures used in the examination of pharmaceutical

materials. In: WHO Expert Committee on Specifications for Pharmaceutical

Preparations. Thirty-second report. Geneva, World Health Organization, 1992.

Annex 5 (WHO Technical Report Series, No. 823); *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, Second updated edition. 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) (http://apps.who.int/medicinedocs/en/q/).