



**PHARMACEUTICAL INSPECTION
CONVENTION PHARMACEUTICAL INSPECTION
CO-OPERATION SCHEME**

PI 038-2

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AIDE-MEMOIRE

**ASSESSMENT OF QUALITY RISK
MANAGEMENT IMPLEMENTATION**

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1. Document history

Adoption by Committee	16 March 2012
Entry into force	2 April 2012

2. Introduction

2.1 The holder of a manufacturing authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation (MA) and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance (QA) incorporating Good Manufacturing Practice (GMP), and thus Quality Control (QC) and Quality Risk Management (QRM). It should be fully documented, and its effectiveness monitored.

2.2 Quality risk management 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. The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

2.3 The harmonised tripartite quality guidelines ICH Q8(R1): Pharmaceutical Development, ICH Q9: Quality Risk Management and ICH Q10: Pharmaceutical Quality System form a set of three documents representing a new approach to pharmaceutical development,

manufacturing, and distribution, often referred to as the paradigm shift initiated by the ICH.

- 2.4 ICH Q9 was adopted in November 2005 as a step 4 document and consecutively on 14 February 2008 introduced as a voluntary Appendix 20 into the EU GMP Guide and on 15 January 2009 into the PIC/S GMP Guide. At the corresponding dates principles of Quality Risk Management (QRM) were in addition introduced in Chapter 1 of both guides. Chapter 2 in EU GMP Part II was updated with QRM requirements on 31 July 2010.
- 2.5 The primary objective for implementing ICH Q9 was to improve the implementation of risk-based approaches / the principles of quality risk management within the pharmaceutical industry and regulatory environment.

3. Purpose

- 3.1 The purpose of this document is to assist GMP inspectors in the assessment of QRM implementation in industry during regulatory inspections. Parts of this Aide-Memoire may also be useful (with suitable modification) during other GXP inspections where similar principles of QRM also apply.
- 3.2 This Aide-Memoire should also contribute to a harmonised approach for inspection of QRM in industry between the different PIC/S Members.

4. Scope

- 4.1 At the time of issue, this document reflected the current state of the art. It is not intended to be a barrier to technical innovation or the pursuit of excellence.
- 4.2 QRM aspects should be an integrated part of the planning and content of all GMP inspections (including for final products as well as for active pharmaceutical ingredients). The existence of this separate Aide-Memoire document does not suggest that specific inspections for QRM systems are performed.
- 4.3 As Annex 20 represents a voluntary standard, this Aide-Memoire relies mainly on the corresponding mandatory articles of Chapter 1 and Annex 15 of the PIC/S GMP Guide.

5. Aide-Memoire

5.1 The Aide-Memoire should be used with the following general comments:

- During an inspection dedicated time is required to be allocated to review the QRM system.
- During a general inspection the inspector should be able to review how the company has integrated QRM without allocating further specific time to the QRM aspects of the inspection.
- References to the GMP Guide given in the row "Reference" refer to the PIC/S GMP Guide Part I.

1. Overall Systems

The purpose of this portion of the Aide-Memoire is to ascertain the extent to which a company can demonstrate that it has a systematic approach to the integration of the principles of QRM into its operational systems, and its endorsement and active support by senior management.

QRM should not be an isolated System of QA; it should be fully embedded into the QA or QM- System.

The QRM process normally consists of several steps including:

- Process mapping identifying all inputs, outputs and existing control measures;
- Risk Assessment (incl. risk- identification, risk-analysis and evaluation);
- Risk Control (including risk reduction and risk Acceptance);
- Communication (i.e. the residual risk should be communicated to the regulators and customers);
- Regular Review of the risks.

These questions seek to gather evidence that:

- The use of QRM is planned;
- The key elements of the QRM program are clearly defined and documented;
- Senior Management provides visible support to QRM;
- Key outcomes of QRM are communicated to and acted upon by Senior Management.

<i>Nr.</i>	<i>Crucial indicators and related questions</i>	<i>Reference</i>
1.1	Is there a high level controlled document describing the company's policies and approach to QRM?	GMP Guide 1 Principle
1.2	Do the key attributes of this document describe how:	
1.3	- What evidence is there that senior management shows commitment to the programme?	ICH Q10 & GMP Guide 1 Principle
1.4	- Responsibilities and functions of key individuals involved in the QRM programme are defined?	GMP Guide: 1 Principle & 1.4(v) & 2
1.5	- The scope, planning and scheduling of QRM activities are organized?	GMP Guide 1.12
1.6	- QRM activities are monitored, evaluated and reviewed for effectiveness?	GMP Guide 1.12
1.7	- QRM activities are authorized and communicated?	GMP Guide 1.12
1.8	- The QRM principles are incorporated into GMP training?	GMP Guide 2 2.11
1.9	- The training requirements for staff directly involved in QRM activities are determined and delivered?	GMP Guide 2 2.10 to 2.14
1.10	- The QRM methodologies are selected and applied?	GMP Guide 1.12
1.11	- The QRM is integrated within the quality system including management of changes to the program?	GMP Guide 1 Principle
1.12	Are systems in place to ensure risks to the quality of the medicinal product are: <ul style="list-style-type: none"> - Assessed? - Controlled? - Communicated? - Reviewed as part of the routine Quality Management Review Process? 	GMP Guide 1.12

2. Expectations on how QRM should be implemented

The level of effort, formality and documentation of the QRM-process should be commensurate with the level of risk. Expectations on the formality and extent of the application of QRM principles during the Inspection will depend upon circumstances and the operations being examined. The conclusions of the risk management process should be justified and documented.

This portion of the Aide-Memoire is intended to gather evidence that the following general principles are applied:

- The basis of any valuable Risk Assessment is **scientific knowledge and experience** with the process being assessed. The basis for the evaluation of the identified and analysed risks is defined by the risk to the patient:
 - Evidence for effectiveness of risk mitigation should be available;
 - Where specific risk elements are discounted this should be supported by appropriate rationale;
 - Evidence supports the decisions made.
- There is a risk that **inappropriate conclusions** may be drawn should assessments be based upon:
 - Unjustified assumptions;
 - Incomplete identification of risk(s) or inadequate information;
 - Lack of relevant experience of the process being assessed and/or inappropriate use of the risk assessment tools.
- The use of **external resource** in assessment can be helpful however:
 - Sole reliance on these may result in inappropriate conclusions or a lack of ownership of the assessment.
 - Any outsourced elements of QRM should be closely evaluated by the inspector and companies discouraged from completely outsourcing their QRM efforts to consultants.
 - There should always be adequate involvement and ownership of risk assessments by staff responsible and accountable for the activities being assessed.

Inspectors should be cautious when reviewing assessments which include other business related risks (e.g. environmental, occupational health & safety) in addition to quality risk assessments. As whilst these factors are important in a holistic sense there is a danger that they may compromise quality.

Nr.	<i>Crucial indicators and related questions</i>	<i>Reference</i>
2.1	Does the Quality Risk Management System ensure that the assessment of the risk to quality:	
2.2	<ul style="list-style-type: none"> - Is based on a systematic identification of risks? - Identifies all reasonably expected risks? 	GMP Guide 1.12
2.3	<ul style="list-style-type: none"> - Takes account of current scientific knowledge and any risk elements discounted are done so from a basis of scientific knowledge and evidence? 	GMP Guide 1.13
2.4	<ul style="list-style-type: none"> - Is conducted in a systematic manner and supported by appropriate evidence for risk mitigation? 	GMP Guide: 1.12 &1.13
2.5	<ul style="list-style-type: none"> - Takes account of experience of the process under assessment? - Does not include any unjustified assumptions? 	GMP Guide 1.13
2.6	<ul style="list-style-type: none"> - Is performed by experienced staff trained in the use of relevant risk assessment tools? 	GMP Guide 1.13
2.7	<ul style="list-style-type: none"> - Is ultimately linked to the protection of the patient? 	GMP Guide 1.13
2.8	<ul style="list-style-type: none"> - Ensures that key steps and decisions are documented with a formality that is commensurate with the level of risk? 	GMP Guide 1.13
2.9	<ul style="list-style-type: none"> - Are periodically reviewed for currency and effectiveness? - Is conducted proactively, retrospectively and reactively as appropriate? 	GMP Guide 1.12
2.10	<ul style="list-style-type: none"> - Ensures where assessments are revised, the changes are clearly visible and tracked? - Has any involvement of external resources been in a facilitating/advising mode rather than doing? - Has the correct balance of ownership by local 	GMP Guide 1.12

Nr.	Crucial indicators and related questions	Reference
	<p>knowledgeable staff been maintained?</p> <ul style="list-style-type: none"> - Are there agreements in place and has the competence of the contract acceptor been adequately assessed by the company where elements of the QRM has been performed by an external party? 	
2.11	<ul style="list-style-type: none"> - Are risk assessments performed sufficiently early to allow appropriate risk mitigation where the risk assessments are being used proactively? 	GMP Guide 1.12
2.12	<ul style="list-style-type: none"> - Supports continual improvement? 	ICH Q10
2.13	<ul style="list-style-type: none"> - Are risks reduced to an acceptable level? - Do the conclusions from the risk assessment reflect the level of risk to the patient? 	GMP Guide 1.13
2.14	<ul style="list-style-type: none"> - Is the level of effort, formality and documentation of the quality risk management process identified and commensurate with the level of risk? 	GMP Guide 1.13

3. Specific areas and activities where implementation of QRM might be expected

The following section provides guidance as to those activities where it would be reasonable to expect to find QRM principles being used in a manner that identifies, prioritises and mitigates risk. GMP Annex 20: (Potential Applications for Quality Risk Management) provides suggestions for implementation. This portion of the Aide-Memoire is intended to guide the inspector

- to those areas where there should be evidence as to extent that QRM has been implemented. Depending upon the maturity of implementation, QRM may be found to be totally absent, partially, superficially, incorrectly applied or fully implemented.
- to the extent that the scope of risk management/ assessments are appropriate and not being used to override GMP and other regulatory requirements.

Nr.	<i>Crucial indicators and related questions</i>	<i>Reference</i>
3.1	To what extent does the company use the potential applications of QRM suggested in ICH Q9?	GMP Guide Annex 20
3.2	Are references included in the controlling procedures or can the company explain how the QRM principles are integrated in the Quality System?	GMP Guide 1 Principle
3.3	The following areas of operation are examples of where there should be evidence of the implementation of QRM principles:	
3.4	- Deviations, OOS-Results, Investigations and CAPA	GMP Guide: 1 Principle & ICH Q10
3.5	- Complaints and recalls	GMP Guide 1 Principle
3.6	<ul style="list-style-type: none"> - Change control <ul style="list-style-type: none"> o Introduction of new manufacturing products or processes o Method and product transfer o Facility and equipment changes 	GMP Guide 1 Principle
3.7	- Method of sampling and testing	
3.8	- Supplier qualification and raw material supply chain	GMP Guide 1

	robustness and supply chain traceability	Principle
3.9	- Validation and qualification	GMP Guide Annex 15
3.10	- Outsourcing and supply chain robustness	GMP Guide: Principle & ICH Q10
3.11	- Reworking and reprocessing	GMP Guide: Principle
3.12	- In process monitoring	GMP Guide: Principle
3.13	- Calibration and maintenance	GMP Guide: Principle
3.14	- Storage and distribution conditions	GMP Guide: Principle
3.15	- Auditing program	GMP Guide: Principle
3.16	- Periodic review of products, processes and procedures	GMP Guide: 1.10 & Principle
3.17	<p>Is there any evidence of QRM being used inappropriately such as:</p> <ul style="list-style-type: none"> - To justify failure to meet regulatory requirements and commitments. - To release batches to market that fall into the category above or to justify increased risk to patient safety from batch deviations. 	

4. Review of residual risk

Following implementation a company should be performing, communicating and documenting periodic reviews of the currency of its risk assessments and outcomes of its risk management plans. This section of the Aide-Memoire looks for evidence that there is a mechanism for routine and triggered review of risk assessments and their associated management plans in the case of significant change or new information coming to light.

A model for Management Review is provided in ICH Q10. A risk register or equivalent is useful to facilitate review by both the company and the inspector.

<i>Nr.</i>	<i>Crucial indicators and related questions</i>	<i>Reference</i>
4.1	Is there a robust system to ensure that all the risk reduction measures (by mitigation or avoidance) have really been implemented in the manner they appear in the risk assessment?	
4.2	<p>Are individual risk assessments and their outcomes reviewed, controlled and re-assessed periodically for currency?</p> <p>Are they still relevant to ongoing circumstances and controls?</p> <p>Is there a mechanism to trigger a review of risk assessments and management plans in the case of significant change or new information from e.g. complaints, investigations, change control etc.?</p>	ICH Q10
4.3	Are the reviews of the risk management plans effective; for example are the following covered:	
4.4	- Frequency	GMP Guide 1.12
4.5	- Responsibilities	GMP Guide 1.12
4.6	- Formality of documentation appropriate to the level of review	GMP Guide: 1.12 & 1.13

4.7	- Visibility and communications of outcomes	GMP Guide 1.12
4.8	- Recommendations and follow up	GMP Guide 1.13

5. Review and improvement of QRM activities

Following implementation a company should be performing, communicating and documenting periodic reviews of the extent to which the QRM system is fully integrated into its activities, and managed and implemented effectively, and to promote continual improvement of the system.

A model for Management Review is provided in ICH Q10.

<i>Nr.</i>	<i>Crucial indicators and related questions</i>	<i>Reference</i>
5.1	Are the QRM processes subject to periodic and triggered review?	
5.2	Are the reviews of the QRM system effective; for example are the following covered:	
5.3	- Frequency	GMP Guide 1.12
5.4	- Responsibilities defined	GMP Guide 1.12
5.5	- Formality of documentation appropriate to the level of review	GMP Guide: 1.12 & 1.13
5.6	- Visibility and communications of outcomes	GMP Guide 1.12
5.7	- Recommendations and follow up	GMP Guide 1.12

6. Revision history

Date	Version Number	Reasons for revision
1 January 2021	PI 038-2	Minor edits to update cross-references to PIC/S GMP Guide (PE 009-14)