Guidance for Industry: Quality Risk Management

Version 1.1

Pharmacy and Poisons Board

Contents

1. Introduction

This guideline is intended to provide general guidance on the interpretation of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* (PIC/S Guide to GMP) with respect to implementing Quality Risk Management (QRM). There may be other acceptable approaches that provide an equivalent level of quality assurance. This guideline is not intended to create additional requirements and is not intended to form the basis for GMP inspections.

Although the *PIC/S Guide to GMP Annex 20* is referenced below, it is recognized that it corresponds to *ICH Q9 Guideline on Quality RiskManagement.*

2. Purpose of this document

To provide guidance to industry when implementing Quality Risk Management.

3. Scope

PIC/S Guide to GMP (Chapter 1, Clauses 1.5 and 1.6) describes QRM as a systematic process to proactively or retrospectively manage risk to product quality using:

- risk assessment;
- risk control;
- risk communication; and
- risk review.

Applying QRM should systematically lead manufacturers through a process to define the risk, based on scientific knowledge and experience with the process under consideration.

The level of effort, formality and documentation of QRM should be commensurate with the level of risk. For example, a minor risk with little potential to impact product quality or patient safety does not require the same rigour as a major risk known to impact patient safety.

Important: QRM should never be used to justify non-compliance with the PIC/S Guide to GMP or any other mandatory requirement from a regulatory authority.

QRM should be applied to all aspects of pharmaceutical quality and throughout the product lifecycle, including (but not limited to):

- product development/Quality by Design (QbD);
- laboratory control and stability testing;
- manufacturing;
- distribution;
- inspection; and
- submission/review processes.

4. What is risk?

The PIC/S Guide to GMP (Annex 20, Clause 8) defines risk as:

"The combination of the probability of occurrence of harm and the severity of that harm."

Applying risk management can be difficult because different people perceive risk differently (risk tolerance). Consequently, a team of diverse stakeholders may attribute:

- different potential risks to a situation or problem;
- different probability of each harm occurring; and
- different severities to each harm.

Although there may be a variety of stakeholders, the protection of the patient by managing the risk should be considered of prime importance.

5. Integrating QRM into Quality Management Systems (QMS)

Risk management should be integrated into the quality systems of the manufacturer's QMS so that QRM is an underpinning process across the whole facility. QRM should not be performed just because the regulator requires it, but it is intended to help:

- ensure product quality;
- provide continued assurance of consumer safety;
- ensure integrity of data;
- ensure regulatory compliance; and
- ensure resources are focused on areas with the greatest quality need.

QRM may be used wherever there is a perceived or real risk. However, the core QMS systems where risk management activities are routinely performed include:

- complaints;
- non-conformances/deviations;
- corrective and preventative actions (CAPA);
- change control;
- internal audits;
- validation;
- supplier evaluation and management; and
- product quality review.

Refer to *Appendix II of Annex 20, PIC/S Guide to GMP PE 009-10*. Note that these examples are guidance only and are not mandatory requirements.

6. Complete a risk assessment

The manufacturer's QRM procedure should indicate the criteria to be used as part of the site QRM model (e.g. number of levels adopted, name used by the site for each level, and description of the level). Criteria should be specified for:

- Consequences/Severity;
- Probability; and
- Detectability (if adopted).

Based on a clear description of the problem(s) a risk assessment considers three fundamental questions:

- What might go wrong?
- What is the likelihood(probability) it will go wrong?
- What are the consequences(severity)?

Establishing a multidisciplinary team is often the best approach to enable the broadest knowledge and experience to be used in considering these questions in an objective way.

Table 1 summarises the stages used during risk assessment that facilitate the answers to the three fundamental questions (above).

Table 1: Stages used during Risk Assessment

Stage	Questions	Description
Risk identification	What might go wrong? What are the possible consequences?	Uses known information, data, experience or stakeholder concerns to identify hazards associated with the risk description.
Risk analysis	What is the likelihood it will go wrong? What is the severity? What is the likelihood it will be detected if it goes wrong?	Estimate the risk associated with the identified hazard(s) – establishes likelihood of occurrence and severity of harm. Either a qualitative or quantitative process may be used (this should be defined when initiating QRM). In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.
Risk evaluation	What might go wrong? What is the likelihood it will go wrong? What are the consequences?	Compare identified and analysed risk against given risk criteria – consider the strength of evidence for the three fundamental questions. This allows priority to be given to the highest risk and identifies what is not acceptable and should be controlled.

The robustness of the data is important because it determines the quality of the output. Understanding any assumptions in the data or sources of uncertainty increases confidence in the output because limitations are identified.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk.

Examples of severity level criteria (Table 2), probability level criteria (Table 3) and a risk evaluation matrix (Table 4) are shown below.

Note: These examples are not intended to show any form of preference in selecting criteria or risk management tools. They are consistent with examples in the *WHO Technical Report 981, Annex 2: WHO guidelines on quality risk management.* This document or *ICH Q9 Briefing Pack* should be consulted for further guidance.

Table 2: Example of Consequence/Severity Levels – the severity levels below are arbitrary examples only. The severity may be assessed either as a quantitative or qualitative ranking.

Severity level (Quantitative)	Severity level (Qualitative)	Example description of consequences
1	Negligible	Will not result in harm requiring attention.
2	Marginal	Results in customer inconvenience and/or harm requiring local first aid treatment.
3	Moderate	Results in serious harm or a customer / community health problem requiring medical treatment.
4	Critical	Results in extensive harm or a customer / community health problem requiring hospitalisation or prolonged medical treatment.
5	Catastrophic	Results in death or extensive harm; a general community health problem attracting public interest and requiring significant medical treatment or hospitalisation for those effected.

Table 3: Example of Probability Levels – probability levels given below are arbitrary examples only.

Probability (Quantitative)	Probability (Qualitative)	Example description of probability (based on events/time)
1	Rare	May occur every 10–30 years
2	Unlikely	May occur every 5-10 years
3	Possible	May occur every 1-5 years
4	Likely	May occur more than once per year
5	Almost certain	May occur several times per year

Table 4: Example of Risk Evaluation Matrix (Risk Classification) – the matrix given below is an arbitrary example only.

		Severity				
		Negligible (1)	**Marginal (2)**	**Moderate (3)**	**Critical (4)**	**Catastrophic (5)**
Probability	**Almost certain (5)**	Medium (5)	High (10)	High (15)	High (20)	High (25)
	Likely (4)	Low (4)	Medium (8)	High (12)	High (16)	High (20)
	Possible (3)	Low (3)	Medium (6)	Medium (9)	High (12)	High (15)
	Unlikely (2)	Low (2)	Low (4)	Medium (6)	Medium (8)	High (10)
	Rare (1)	Low (1)	Low (2)	Low (3)	Low (4)	Medium (5)

The number of criteria levels for severity and probability (Tables 2 and 3 in this example) should be included within the risk evaluation matrix.

The shading in the table represents an example of how the risk classification can be assigned a high, medium or low status. If a quantitative model is used, the severity and probability levels can be multiplied to calculate a Risk Priority Number (RPN) and this can be used to determine the risk classification. In the example above:

RPN ≤ 4 = Low risk classification

RPN 5 – 9 = Medium risk classification

RPN ≥ 10 = High risk classification

Information on how the risk classification will be determined should be included in the relevant procedure.

7. Implement risk control

Risk control measures should be identified to reduce any risk determined to be unacceptable, to an acceptable level. Risk control should take the following into consideration:

- What can be done to reduce, control or eliminate the risk?
- Will the risk control measures be effective?
- Are new risks introduced with risk controls?
- Is the risk acceptable once controlled or does the risk require further control?

In the example above (Table 4):

If the risk is determined to be "low", this normally means that the risk is acceptable and risk control is not required.

If the risk is determined to be "medium", it should be decided whether it is acceptable or unacceptable. If unacceptable, appropriate risk control measures should be implemented. Justification for those determined to be acceptable should be documented and if risk control is not considered necessary, the justification for this should also be documented.

If the risk is determined to be "high", risk control is required and priority should be given.

8. Routine risk review

QRM should be integrated into the quality management processes, including mechanisms to:

- review risk assessments over time, taking into consideration any new knowledge or experience;
- continue to use the same approach for events that might have an impact on the original quality risk management decision – including planned events (e.g. results of product review, inspections, audits, change control) or unplanned events (e.g. root cause from failure investigations, recall);
- determine the frequency of reviews based on the level of risk; and
- reconsider risk acceptance decisions.

9. Risk analysis tools

Different QRM tools may be used for different types of situations or levels of risk. No one tool is recommended and an effective tool for the situation should be selected. Staff involved in risk management activities should be adequately trained in using the tools.

There are a variety of recognised tools that may be used to implement QRM within the pharmaceutical industry. PIC/S Guide to GMP, Annex 20 includes a list of those commonly used. Further useful information on the selection and use of specific tools may be found in the *WHO Technical Report 981 Annex 2: WHO guidelines on quality risk management* and also in the *ICH Q9 Briefing Pack.*

10. Characteristics of good QRM

Table 5 summarizes some key elements of good QRM.

Table 5: Characteristics of good QRM

QRM Element	Examples
Clearly defined risk statement(s)	• Clearly identify the process being assessed and what it is attempting to achieve • Based on systematic identification of possible risks • Identifies all reasonably expected risks with a factual assessment and mitigation where required • Determines what the harm/risk is and what the impact could be on the patient and the likelihood of occurrence • Contains objective risk reduction plans
Scientifically-justifiable	• Take full account of current scientific knowledge • Use factual evidence supported by expert assessment to reach conclusions • Do not include any unjustified assumptions • Ultimately be linked to the protection of the patient
Staff with appropriate product/process knowledge and experience	• Facilitated by staff with experience in the site QRM procedure and the process being risk assessed
Level of effort is commensurate with the level of risk	• Be conducted and documented to an appropriate level commensurate with risk

Quality oversight	• Appropriate staff approve the QRM approach and the documentation generated throughout the QRM process • All QRM records are appropriately controlled

Document Information

Version	Date	Description of Change
1.0	27 Dec 2013	First version
1.1	Sept 2024	Reformatting of version 1.0

References

Document Title
ICH Q9: Quality Risk Management
ICH Q9: Briefing Pack
PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE 009-10: Annex 20 Quality Risk Management
PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE 009-10: Part I and II
WHO Technical Report 981 Annex 2: WHO guidelines on quality risk management

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