Quality Risk Management Principles and Industry Case Studies

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ABSTRACT: The Pharmaceutical Quality Research Institute Manufacturing Technology Committee (PQRI-MTC) commissioned a Risk Management working group to assemble industry case studies for the purpose of advancing the understanding and application of ICH Q9. The working group was comprised of eight representatives from industry and US-FDA with risk management experience and expertise. This paper represents the outcome of the Risk Management Working Group and provides a summary of common risk management principles and best practices, several working tools to foster consistency around the use of ICH Q9 in day-to-day risk management decision-making, and a series of examples of risk management applications currently in use by major pharmaceutical firms.

KEYWORDS: Effective Risk Management, ICH Q9, Failure Mode Effect Analysis, Risk Ranking, Quality Risk Management Principles, Quality Risk Management Case Studies.

Introduction

ICH Q9 - *Quality Risk Management* provides an excellent high-level framework for the use of risk management in pharmaceutical product development and manufacturing quality decision-making applications. It is a landmark document in acknowledging risk management as a standard and acceptable quality system practice to facilitate good decision-making with regard to risk identification, resource prioritization, and risk mitigation / elimination, as appropriate.

Recognizing the need to propagate and expedite holistic adoption of Quality Risk Management across the pharmaceutical industry, the Pharmaceutical Quality Research Institute Manufacturing Technology Committee (PQRI-MTC) commissioned a small working group of industry and FDA representatives to seek out good case studies of actual risk management practices used by large PhRMA and Bio-Pharmaceutical firms for the purpose of sharing with the industry at large.

The working group spent approximately one year soliciting risk management case studies from industry peers and contacts. Greater than twenty risk management examples were reviewed by working group members. Each study was graded against six criteria to assess applicability, usefulness and alignment to ICH Q9, and the resulting set of highest graded cases studies were subsequently measured against two additional criteria to ensure a balanced mix of examples for this report (re: Table I - *Risk Management Case Study Assessment Criteria*). The resulting eight highest graded cases studies are provided under **Case Studies** below. Due to the size of a well developed risk assessment, especially when applied to a complex problem or operating area, the presented case studies in most instances represent redacted versions of the actual assessment. Nonetheless, the provided summaries are effective in demonstrating the general thought process, risk application and use of the chosen risk methodology without over-complicating the example with the detailed line-by-line specifics of the actual assessment itself.

As a by-product of the Working Group's collaboration on risk management practices, several common principles emerged which are reflective of current industry and regulatory thinking. These principles are aligned with, and in some instances expand beyond, those already defined by ICH Q9 and are included in this report. In addition, several risk management reference tools in use by participating firms were found to be useful in guiding the understanding and application of good risk management practices and have been included herein as well.

Table 1: Risk Management Case Study Assessment Criteria

***To be assessed for each case study*:**

1. Case study can be tied to one or more core GMP Systems.
2. Case study addresses a recognized area of general industry interest / application.
3. Case study uses an approach that is consistent with ICH Q9 concepts and direction.
4. Case study utilizes recognized quality risk management tools.
5. Case study is appropriately simple and succinct to assure clear understanding.
6. Case study provides areas for decreased and increased response actions.

***To access case study choices in aggregate*:**

7. Case study avoids excessive redundancy in subject and tools as compared to other planned models.
8. Case study balances use of quantitative and semi-quantitative tools.

Scope

Risk management principles, case studies, and supporting tools currently in use by large pharmaceutical manufacturers for effective quality oversight of product development and manufacturing operations are included in this report. For each case study, the applicable corresponding quality system (*Quality, Facilities & Engineering, Material, Production, Packaging & Labeling,* or *Laboratory Control*) consistent with FDA's quality systems guidance document and the risk methodology employed has been identified for ease of categorization, understanding and potential application by the reader. There are no medical device examples included in this report, although the case studies and tools shared herein are equally relevant to device manufacturing.

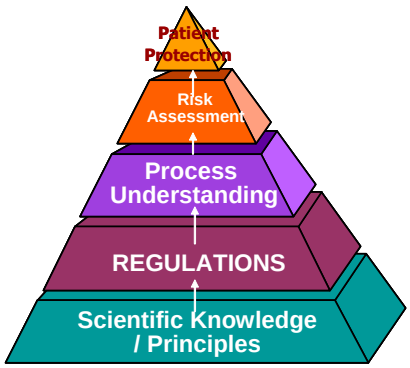
Principles / Common Practices

Core principles of risk management include the follow general tenants:

1. *Compliance with applicable laws is an absolute requirement* - Risk assessment is to be used to assess how to assure compliance and the resulting prioritization for action -- not for a decision regarding the need to fulfill applicable regulations or other legal requirements.
2. *Risk can only be effectively managed when it is identified, assessed, considered for further mitigation and communicated* - This principle embodies the four general stages to an effective quality risk management process as defined by ICH Q9: 1) Risk Assessment (to include risk identification, analysis, and evaluation, 2) Risk Control (to include risk reduction and acceptance), 3) Risk Communication, and 4) Risk Review.

3. *All quality risk evaluations must be based on scientific and process-specific knowledge and ultimately linked primarily to the protection of the patient* - Risk assessment is based on the strong understanding of the underlying science, applicable regulations and related processes involved with the risk under analysis. Collectively, these components are to be assessed first and foremost with regard to the potential impact to the patient (re: Diagram 1- *Quality Risk Evaluation Pyramid*).

Diagram 1: *Quality Risk Evaluation Pyramid*



4. *Effective risk management requires a sufficient understanding of the business, the potential impact of the risk, and ownership of the results of any risk management assessment.*
5. *Risk assessment must take into account the probability of a negative event in combination with the severity of that event* – This principle also serves a useful working definition for risk (i.e., risk represents the combination of the probability and severity of any given event).
6. *It is not necessary or appropriate to always use a formal risk management process (e.g., standardized tools); the use of informal risk management processes (e.g., empirical assessment) is acceptable for areas of less complexity and lower potential risk* – In general, risk decisions are made by industry every day, in the course of regular business. The complexity of the events surrounding each decision and the potential risk involved are important inputs in determining the appropriate risk assessment methodology and corresponding level of analysis required to ensure the appropriate risk decision is made. For the less complex and/or those decisions involving little risk, a qualitative analysis (e.g., decision tree) of the options may be all that is required. Generally, as the complexity and/or risk increases, so should the sophistication of the risk assessment tool used to facilitate the corresponding analysis.
7. *The level of documentation of the risk management process to render an appropriate risk assessment should be commensurate with the level of risk.* (Re: Diagram 2 - *Documentation Level*).

Diagram 2: Documentation *Level*

Risk Assessment Supporting Tools

A key early step in the execution of a risk analysis is to determine the appropriate risk assessment tool (or methodology). There is generally no single best choice for any given assessment process, and the selection of the appropriate risk methodology should be based on the depth of analysis required, complexity of the subject risk of concern, and the familiarity with the assessment tool. Based on the industry examples reviewed by the Working Group, *Risk Ranking & Filtering* (sometimes referred to as *Risk Matrix*) and *Flowcharting* were the most popular tools used for basic risk assessment activities. Correspondingly, *Failure Mode Effect Analysis* appeared to be the most frequently used methodology for more advanced risk analysis efforts. Some examples demonstrated the power of combining tools to help in more complex analysis. For example, Fault Tree Analysis (FTA) or a Fish-bone diagram can be used to initially

scope and evaluate the fault modes of a particular problem and then be used to feed a Hazards Analysis and Critical Control Point (HACCP) or similar tool to evaluate overall system control and effectiveness.

A list of generally well-recognized risk management tools is provided in Table II – *Common Risk Management Tools*, to facilitate the reader's evaluation of potential alternatives. While the list is not inclusive of all available risk assessment methodologies, it represents some of the more frequently used approaches.

Table II – Common Risk Management Tools

Risk Management Tool[1]	Description / Attributes	Potential Applications[2]
Basic Tools		
Diagram Analysis • Flowcharts • Check Sheets • Process Mapping • Cause/Effect Diagrams	▪ Simple techniques that are commonly used to gather/organize data, structure risk management processes, and facilitate decision making.	✓ Compilation of observations, trends, or other empirical information to support a variety of less complex deviations, complaints, defects, or other circumstances.
Risk Ranking and Filtering	▪ Method to compare and rank risks ▪ Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk scores.	✓ Prioritize operating areas / sites for audit/assessment. ✓ Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool.
Advanced Tools		
Fault Tree Analysis (FTA)	▪ Method used to identify all root causes of an assumed failure or problem. ▪ Used to evaluate system/sub-system failures one at a time, but can combine multiple causes of failure by identifying causal chains. ▪ Relies heavily on full process understanding to identify causal factors.	✓ Investigate product complaints ✓ Evaluate deviations.
Hazard Operability Analysis (HAZOP)	▪ Tool assumes that risk events are caused by deviations from the design and operating intentions ▪ Uses a systematic technique to help identify potential deviations from normal use or design intentions.	✓ Access manufacturing processes, facilities, and equipment ✓ Commonly used to evaluate process safety hazards.
Hazards Analysis and Critical Control Points (HACCP)	▪ Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring ▪ Bottom-up approach that considers how to prevent hazards from occurring and/or propagating ▪ Emphasizes strength of preventive controls rather than ability to detect ▪ Assumes comprehensive understanding of the process and that critical process parameters (CPPs) have been defined prior to initiating the assessment. Tool ensures that critical process parameters will be met.	✓ Better for preventive applications rather than reactive ✓ Great precursor or complement to process validation ✓ Assessment of the efficacy of CPPs and the ability to consistently execute them for any process
Failure Mode Effects Analysis (FMEA)	▪ Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance. ▪ Once failure modes are known, risk reduction actions can be applied to eliminate, reduce, or control potential failures. ▪ Highly dependent upon strong understanding of product, process and/or facility under evaluation. ▪ Output is a relative "risk score" for each failure mode.	✓ Evaluate equipment and facilities; analyze a manufacturing process to identify high risk steps/critical parameters.

[1] Sample list of key risk management tools – others (not listed here) may apply for a specific application

[2] Examples only

Each risk subject and assessment warrants consideration of the applicable descriptors of potential risk and related consequences. Ideally, firms should establish a guidance document ahead of any risk analysis, such as the one provided in Table III - *Severity Categorization Table*, to help guide the risk assessment process and guide consistency in decision-making company-wide.

Table III – "Severity Categorization Table"

Severity of Consequences	Category			
	Patient Safety	**Regulatory Compliance**	**Product Supply**	**Other**
5 - Catastrophic	Use of product will cause a serious health consequence. Patient safety is affected by product safety that is either a function of product design or a manufacturing defect.	Consent decree, product seizure, regulatory-imposed cessation of operations or equivalent.	Market stock out (patient impact) of medically significant products.	↑ Subject specific issues may warrant the consideration of other regulatory or business impacts e.g.: • company reputation • "current" GMP practices within industry • evolving regulations Differentiation around the severity of consequences may also need to include these or other areas of interest / potential impact as well. ↓
4 - Very Serious	Use of product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. Degree of seriousness is subject specific.	Major observations or regulatory warning letter. Practices/facility not aligned with regulatory requirements, and there is no technical justification for approach. GMP license in jeopardy of being suspended or withheld.	Market stock out (patient impact) of non-medically significant products.	
3 - Serious		Repeated and/or multiple minor observations. Practices and/or facility not aligned with current GMP expectations, but there is technical justification for the site's approach.		
2 - Important	Highly unlikely that use of product will cause an adverse health consequence.	Few minor observations / comments. System gaps.	Product back-orders (no patient impact) resulting in active efforts to allocate supply to avoid patient impact.	
1- Noticeable	No probability of patient impact.	One-off audit findings. Minor system gaps.	Product backorders (no patient impact) resulting in temporary shortage to wholesalers.	

Case Studies

Eight industry examples of quality risk assessment applications are provided below. These case studies were selected against a core set of criteria (see **Introduction** above) designed to identify models that embody the intent and spirit of ICH Q9. These examples address real-life issues, are straightforward in their application and are designed to engender a general understanding and appreciation of the usefulness of risk management applications in routine decision-making opportunities. As noted above, given size and complexity, the presented case studies are often redacted versions of the actual assessment. Nonetheless, sufficient information has been provided in each example to demonstrate the concept, application, and use of fundamental risk principles in the assessment effort.

By far, the greatest number of systems represented in the collected case studies from contributing industry firms were for risk assessments performed for manufacturing *Quality System* and *Facilities & Engineering System* needs (9 total case studies evaluated, of which 7 are

included in this report). Several case studies represented risk assessment work performed as part of product development (4 total cases assessed, of which 1 graded high enough to be included in this report). Of the case studies evaluated, the most commonly used basic risk management facilitation methods were flowcharts, check sheets, and risk ranking. For more sophisticated analysis needs, Failure Mode Effect Analysis (FMEA) and Hazards Analysis and Critical Control Points (HACCP) methodologies were the most common tools applied. A few of the case studies evaluated made use of more than one risk analysis tool and, in one instance, a modified version of a standard risk methodology for purposes of simplifying the analysis.

While the authors have attempted to include case studies that represent approaches that appear to be consistent with current good manufacturing practices, the content and decisions made by each risk assessment exercise represent the opinions of the authoring firm. As such, inclusion here is not intended to codify the resulting individual conclusions from a quality perspective, which would have required, at least for some of the models, a greater degree of familiarity with the specific applications, data inputs, and subject matter, and was not within the scope of the initiative. Rather, inclusion here indicates that the example represents a perceived area of quality interest and a functional and actual example of risk management employed towards effective analysis, problem-solving and decision management.

The risk assessment case studies are summarized in the following list and are accessible by opening the corresponding attached files. Each case study is organized in similar fashion according to the following general sequence:

- **Introduction / Background** - A brief summary is provided of the area of required risk assessment.
- **Risk Question** - The first step in the Quality Risk Management (QRM) process is to develop and agree upon the *Risk Question*. In the development of the *Risk Question*, it is important to first consider if there is any potential impact of the proposed actions to the patient. Evaluation of risks, when applicable, should ultimately be linked to the protection of the patient. Clearly defining the *Risk Question* facilitates selection of the appropriate tool, identifies relevant data, information and assumptions, assists in the identification of resources, responsibilities and accountabilities, and ensures that appropriate focus on the business objective is maintained.
- **Risk Tool Selection** - The selected *Risk Assessment Method or Tool* will be used to organize data, understand what steps can be taken to reduce or control risk and to help make appropriate decisions. In the selection of a *Risk Assessment Method*, it is recommended to evaluate the QRM process and to select the simplest tool available to support the process.
- **Risk Assessment (**Risk Identification and Risk Analysis and Evaluation) - The objective of *Risk Identification* is to develop a comprehensive analysis to include all applicable operations. At this stage of the QRM process, care should be taken to not exclude those operations which may be simply perceived as 'low risk', without fully evaluating the actual potential influences and associated potential risks involved. The *Risk Analysis* stage of the QRM process estimates the potential harm(s) associated with each potential risk. The analysis may be qualitative or quantitative in nature, or a combination of the two.

- **Risk Control** - During the *Risk Control* stage of the QRM process, a decision is made on which risks, if any, require mitigation and the necessary actions are taken in order to reduce or avoid all prioritized risks, as appropriate and practical.
- **Risk Documentation and Communication** - Communication of the QRM process should fully integrate key stakeholders into the QRM process. By ensuring that key stakeholders are engaged in both the data collection process for the Risk Assessment and the decision-making for Risk Control, the probability of organizational buy-in and support is maximized. The output of the QRM process and associated risk analysis justifying the approach, should be *documented* and endorsed by the site quality unit. Additionally, this information should be *communicated* to stakeholders for their information and to ensure their support.
- **Risk Review** - Appropriate systems should be in place to ensure that the output of the QRM process is periodically *reviewed*, as appropriate, to assess new information that may impact the original QRM decision. Examples of changes that may potentially impact risk of site operational systems include: changes to control systems, changes to equipment and processes, changes in suppliers/contractors, organizational restructuring, etc.

1. Case Study No: RMWG-01
   Title: **Internal GMP Auditing**
   System: Quality Risk Tool: Risk Ranking & Filtering
   Brief Description: Risk assessment used to optimize audit schedule to focus on prioritized needs.
   Link: [*see attached Case Study RMWG-O1 Internal GMP Auditing*]

2. Case Study No: RMWG-02
   Title: **Non-Sterile Facility Cleaning Requirements**
   System: Quality Risk Tool: Decision Tree and Risk Matrix
   Brief Description: Risk assessment used to define minimum cleaning requirements (excludes aseptic and potent compounds).
   Link: [*see attached Case Study RMWG-O2 Non-Sterile Facility Cleaning Requirements*]

3. Case Study No: RMWG-03
   Title: **Functional Equivalence for Equipment Replacements**
   System: Facilities & Engineering Risk Tool: FTA
   Brief Description: Risk-based approach used to define a functional equivalence assessment process.
   Link: [*see attached Case Study RMWG-O3 Functional Equivalence for Equipment Replacements*]

4. Case Study No: RMWG-04
   Title: **Facility Bio-containment Inactivation**
   System: Quality Risk Tool: HACCP
   Brief Description: Risk assessment used to identify and control potential cross-contamination.
   Link: [*see attached Case Study RMWG-O4 Facility Bio-containment Inactivation*]

5. Case Study No: RMWG-05
   Title: **Packaging Line GMP Optimization**
   System: Packaging Risk Tool: FFEA (FMEA modified)
   Brief Description: Risk assessment used to review and optimize packaging line quality performance.
   Link: [see attached Case Study RMWG-O5 Packaging Line GMP Optimization]

6. Case Study No: RMWG-06
   Title: **Pack-Out Remedies to Minimize Contamination and Exposure**
   System: Facilities & Equipment Risk Tool: Evaluation table / HAZOP elements
   Brief Description: Risk-based assessment to identify and remediate contamination and occupational concerns with the packing of a non-sterile API.
   Link: [see attached Case Study RMWG-O6 Pack-Out Remedies to Minimize Contamination and Exposure]

7. Case Study No: RMWG-07
   Title: **Defining Process Space**
   System: Other (Product Development) Risk Tool: FMEA
   Brief Description: Risk-methodology used to define factors with greatest potential to impact product performance (QbD development).
   Link: [see attached Case Study RMWG-O7 Defining Process Space]

8. Case Study No: RMWG-08
   Title: **Process Deviation Analysis (Empty Capsules)**
   System: Quality Risk Tool: FMEA
   Brief Description: Risk assessment used to evaluate impact of a process deviation related to a small number of empty capsules.
   Link: [see attached Case Study RMWG-O8 Process Deviation Analysis]

Risk Tool Trainers: In assembling this collection of case studies, the document authors recognized that it may also be beneficial to provide some additional background on several of the core risk methodologies. Included herein are fundamental trainers for the application of "Risk Ranking & Filtering"; "Failure Mode Effect Analysis (FMEA)"; "Hazard & Operability Analysis (HAZOP)"; and "Fault Tree Analysis (FTA)". These are intended to be high level trainers to facilitate greater familiarity with the risk methodology used for the corresponding case study.

Risk Tool Trainers

Risk Ranking & Filtering	FMEA	HAZOP	HACCP
Link: [see attached Risk Tool: Risk Ranking & Filtering]	Link: [see attached Risk Tool: FMEA]	Link: [see attached Risk Tool: HAZOP	Link: [see attached Risk Tool: HACCP

Summary

The Risk Management Working Group was successful in soliciting a meaningful database of case studies that graded high against pre-defined core criteria designed to identify current quality risk assessment examples that were aligned to ICH Q9 principles. A subset of the studies reviewed were determined to be useful working examples for purposes of promulgating good risk management practices for quality decision making.

Eight case studies, representing a range of quality-specific applications and risk management tools, were identified and structured into a standard format for easy review and subsequent training applications, as appropriate. The greatest number of case studies reviewed by the Working Group addressed Quality System (e.g., auditing) and Facilities and Equipment System (e.g., equipment equivalency) needs. The most popular tools used were Risk Ranking / Matrix, Failure Mode Effect Analysis, and Hazard Analysis and Critical Control Points (HACCP).

The collected case studies demonstrate that there is a wide range of applications for the use of structured risk management analysis to facilitate effective quality decision activities. The studies demonstrate the baseline need to choose the appropriate risk methodology for the targeted need, taking into account the degree of complexity and risk involved for the specific subject of concern. It is equally important to pre-define the potential resulting risk categorizations so as to not be influenced by the assessment results in defining appropriate response actions. Finally, once risks have been appropriately assessed and prioritized, clear risk mitigating actions must be defined, communicated, implemented and monitored for effectiveness.

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