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Advancing competency in managing risk and knowledge: Steps toward operationalisation of the Risk-Knowledge Infinity Cycle (RKI Cycle) Part 3: Uncovering knowledge for QRM through knowledge mapping at node 1

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Advancing competency in managing risk and knowledge: Steps toward operationalisation of the *Risk-Knowledge Infinity Cycle* (*RKI Cycle*)

Part 3: Uncovering knowledge for QRM through knowledge mapping at node 1

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Abstract

To date, literature on the *Risk-Knowledge Infinity Cycle* (*RKI Cycle)* has mainly been theoretical. This paper series intent is to focus on the operationalisation of the *RKI Cycle* by describing a series of steps – the "How to" – for *RKI Cycle* deployment, to help move the *RKI Cycle* from theory to practice. The third paper in this series focuses on ensuring the best available knowledge flows into QRM through a case study demonstrating knowledge mapping to support effective quality risk assessment during commissioning and qualification activities.

Introduction

This paper is the third of a planned series of articles looking at how to build competency in managing risk and through operationalisation of the *Risk-Knowledge Infinity Cycle* (*RKI Cycle*) and associated principles. The intent is to take the theoretical concepts published to date on the *RKI Cycle* and provide tangible steps of how it can be applied, along with supporting examples.

Importantly, the parts in this series are not intended to be sequential nor are the required steps to operationalisation; instead, readers can selectively explore individual topics. It is intended at the conclusion of the series a relationship map will be developed to connect all of the parts in the series.

This paper focuses specifically on the development of a knowledge map for node 1 of the *RKI Cycle* to support quality risk (QRM) management activities conducted during node 2 of the *RKI Cycle*.

Other papers in this series are planned to address the operationalisation of the *RKI Cycle* for other important processes in the pharmaceutical lifecycle, such as change management, technology transfer, and others.

RKI Cycle Node 1: Ensuring the best available knowledge flows into QRM

The following figure presents a summary of the *RKI Cycle* [1], it's key supporting concepts and how the *RKI Cycle* can be applied to enable ICH Q10 [2] with the co-enabler of risk management (Figure 1).

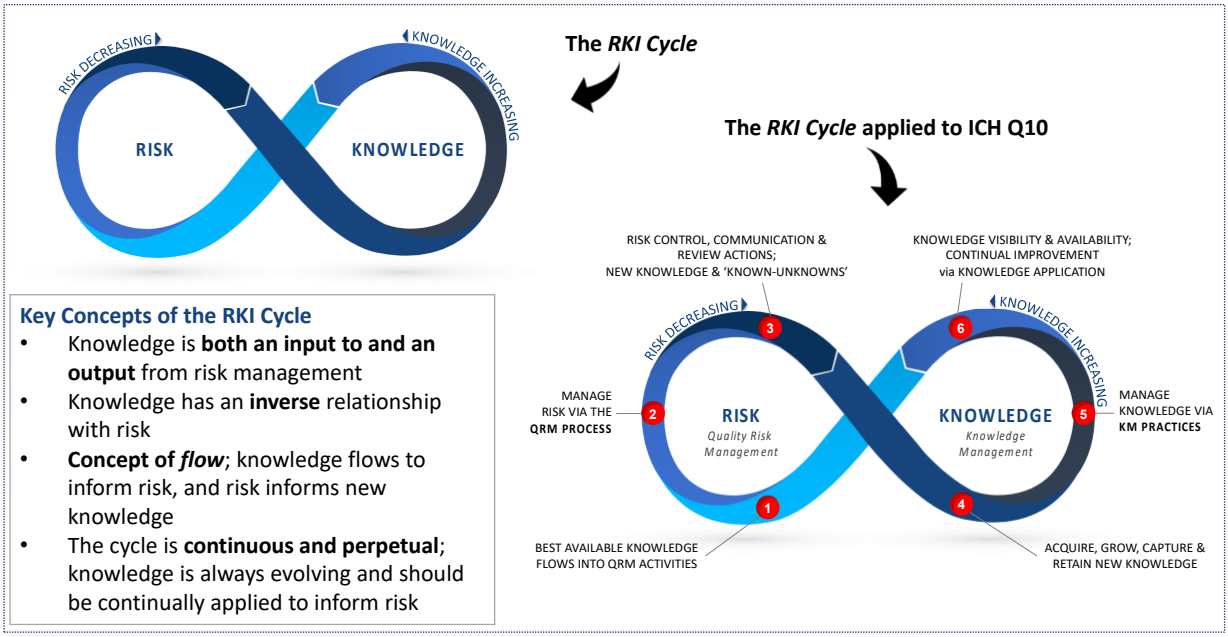

Figure 1 - An Introduction to the RKI Cycle [1]

In considering ICH Q10, the *RKI Cycle* proposes a series of 6 principles, one for each of the 6 nodes on the *RKI Cycle* [3]. The principle for Node 1 is to *ensure the best available knowledge flows into QRM activities*. This paper outlines how knowledge mapping can be applied as a practical step to address this principle in support of a larger effort to operationalise the *RKI Cycle*.

An introduction to *Knowledge Mapping*

Knowledge mapping is a technique which is used to clearly identify the knowledge that is relevant to a defined scope (e.g., a technology transfer) and to assess the availability of such knowledge (i.e., can the knowledge be found efficiently and effectively) to complete the technology transfer.

The basic steps involved with knowledge mapping are as follows [4], [5]:

1. *Define the scope*: This could be a process (e.g., the process for technology transfer) or the functional area (e.g.., a department such as the engineering unit at a manufacturing)

2. *Determine what knowledge is needed* or otherwise associated for the given scope, considering both explicit knowledge and tacit knowledge [1], as tacit knowledge makes up 70 to 80% of the knowledge in an organization [6], [7].
3. *Assess how effectively and efficiently the knowledge supports the process* or *functional area*. For example, does the knowledge easily 'flow' into the process or functional area on demand? Is it available and accessible without heroics? Does everyone know where to go get the knowledge?
4. *Evaluate and prioritise opportunities for improvement*, which typically result in a having a positive impact to the specified scope (e.g., reduced effort, reduced cycle time, improved quality, reduced risk, improved employee engagement, etc.)

Case Study: Knowledge to support quality risk assessment during commissioning & qualification

Focusing on node 1 of the *RKI Cycle,* and using the knowledge mapping technique to *ensure the best available knowledge flows into QRM*, the following practical steps can be applied as outlined below.

Step 1: Define the scope

The first activity in quality risk management is typically performing a quality risk assessment (QRA) [8] as shown in Figure 2. Therefore, to limit complexity, the scope for this knowledge mapping exercise is the QRA process within QRM.

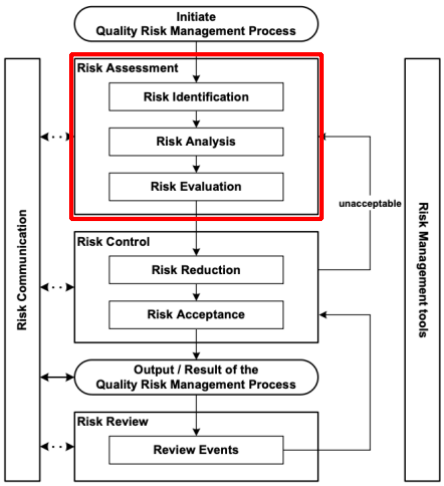

Figure 2 - Quality risk assessment, as the first step within QRM [8]

In order further focus the scope for this case study, the scope is specifically on QRA for commissioning and qualification (C&Q) activities. C&Q was selected as these are generally mature and well-defined events in the pharmaceutical industry. However, it should be noted

[1] Explicit knowledge is codified knowledge, such as a document or image, while tacit knowledge refers to knowledge that resides in the minds of individuals and is surfaced in response to a situation or action [18]. Tacit knowledge is often referred to as 'know-how'.

that the knowledge mapping process is the same regardless of the specifics of the scope selected.

Step 2: Determine what knowledge is needed

Knowledge and information – in both explicit and tacit forms – are a fundamental input to the QRA process as they inform the fundamental questions posed by QRM [8], including:

- What might go wrong?
- What is the likelihood it will go wrong?
- What are the consequences if it does go wrong"

In the case of C&Q as an exemplar, several guidance documents detail sources of information and knowledge that may inform QRM. While not an exhaustive list of guidance, the authors reviewed in detail the following documents for sources of information and knowledge pertinent to QRA.

- PMBOK Guide, by Project Management Institute [9]
- Risk-Based Manufacture of Pharmaceutical Products, a Baseline Pharmaceutical Engineering guide by ISPE [10]
- Commissioning and Qualification, a Baseline Pharmaceutical Engineering guide by ISPE [11]
- Change Management System as a Key Element of a Pharmaceutical Quality System (Part 3), a Product Quality Lifecycle Implementation guide by ISPE [12]
- Corrective Action and Preventative Action (CAPA) System, an Advancing Pharmaceutical Quality guide by ISPE [13]
- Annex 15: Qualification and Validation of the EudraLex Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use [14]
- Quality Risk Management Q9(R1) Step 2 (draft), by ICH [15]
- Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development and Operation of PAT Processes for Pharmaceutical Manufacture, ASTM E2476-16 [16]
- Standard Guide for Specification, Design and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment, ASTM E2500-13 [17]

This analysis identified at least 57 sources of knowledge which may inform QRA. These sources were grouped into 6 categories for simplification as follows:

- Product Knowledge
- Regulatory Requirements
- Pharmaceutical Quality System (PQS) Knowledge
- Project Capability
- QRM Knowledge
- Process Knowledge

The complete listing of the 57 sources of knowledge is presented in Figure 3, which include many examples of explicit knowledge but also many perhaps less obvious examples of tacit

knowledge, including such tacit knowledge inherent in experts, prior experience, know how, history and lessons learned.

Product Knowledge	Regulatory Requirements	PQS Knowledge	Project Capability	QRM Knowledge
• Lifecycle documents • Specifications/ Acceptance Criteria – Product • Specifications/ Acceptance Criteria – Materials • Design/ Validation Documents - Measurement & Analysis Systems • History of Product Issues (Product under analysis or related) • Supply Chain (Product & Materials) • Toxicology Data/ Acceptable Daily Exposure (ADE) Value • Information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment; • Degradation Pathways/ Stability Data	• Applicable Legislation, Laws, EHS, etc. • Guidance/Best Practice Documents • Pharmacopeial and Test Standards • Submitted/ Approved Regulatory Filings	• Change Management Strategy • PQS Procedures - Process under analysis • Quality Records • Maintenance Records • Validation Procedures and Policies • Supplier Management/Procurement P&Ps • CAPA Data - Complaints/ audits/ Deviations/ Trends • APR/Management Reviews • Business Strategy/Priority for Product	• Contracts/Scope/Turn-Over-Packages • C&Q Plans/Schedules • Capabilities & Resources • Laboratory Support Capabilities • Training Procedures and Policies • Good Engineering Practice • Roles & Responsibilities • EHS Documents -Safety Data • Conflicting Objectives/Requirements • KM Outputs (Legacy Requirements)	• Risk Management Knowledge • Risk Management Procedures and Policies • Defined Risk Question/Scope • Trained RM Practitioners/Facilitators • Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

Process Knowledge	
• Process User Requirements • Specifications/ Acceptance Criteria - Process • Design/ Validation Documents - Facility & Utilities • Design/ Validation Documents - Process and Equipment • Design/ Validation Documents - Process Controls • Design/ Validation Documents - Measurement & Analysis Systems • Design/ Validation Documents - Software Systems • Design/ Validation Documents - Cleaning • History of Problems with process/outputs	• Drawings • Calibration Requirements • QRM Documents from design/previous stages • System Integration Requirements • Equipment Manuals/ Technical Specifications • Materials of Construction • Process Capability/Performance Indices • Routes for Contamination/Cross Contamination • Cleaning Process Performance Capability • Training & Competence in Process • Prior Knowledge/Lessons Learnt - current or other locations

Figure 3 - Illustrative sources of knowledge for C&Q risk assessment

Step 3: Assess how effectively and efficiently the knowledge supports the process

With the sources of knowledge identified, the next step in knowledge mapping is an assessment of how the knowledge supports the process, which in this case study is QRA at C&Q. Although there is no definitive and singular means of assessment, the authors propose assessing two attributes: *flow* and *quality*.

- *Flow of knowledge* is defined as the extent to which the knowledge is available and accessible on demand when needed for the process. Thought starter questions to aid in this assessment include:
  - Are heroics needed to find or access the knowledge?
  - Can a newcomer figure it out quickly?
- *Quality of knowledge* is defined as the extent to which the knowledge is reliable for its intended use. Thought starter questions to aid in this assessment include:
  - Is there sufficient context and supporting rationale for the knowledge
  - Is it complete and accurate (for intended use)

With these attributes defined, a scale is required to assign an assessment rating to judge the flow and quality of knowledge (i.e., good to not good). The authors propose a qualitative three-tier scale of *excellent-marginal-poor* as follows:

- *Excellen*t: suggests the knowledge flow and quality are robust, broadly understood and consistent.
- *Margina*l: suggests a potentially satisfactory state, but likely with some lack of consistency and an opportunity to improve efficiency and/or effectiveness of

knowledge flow and/or quality. This could also suggest variability across groups or individuals, with some having no issues and others having difficulty.

- *Poor*: suggests significant challenges and likely negative process impacts due to knowledge flow (e.g., it cannot be found or takes a long time) or quality (e.g., perhaps one cannot locate the most recent version). In these cases, there are delays or incomplete knowledge is applied, leading to sub-optimal risk assessments and decision making.

The following rubric prepared by the authors (Figure 4) summarises these attributes of knowledge flow and quality, the rating scale, and specific definitions for each level.

Rating \ Attribute	***FLOW*** **of knowledge** - **Available, accessable, on demand**? - Are **heroics** needed? - Can a **newcomer** figure it out quickly?	***QUALITY*** **of knowledge** - **Reliable** (for intended use)? - Sufficient **Context & Rationale**? - Is it **Complete & Accurate**?
Excellent	Flows readily. You get what you need on demand, when and where needed. Processes are in place.	Meets all criteria as expected (no lacking context, rationale, etc.)
Marginal	Minor issues or inefficiency but can get what is needed without wasting much time or energy	Minor issues requiring simple clarification or explanation with no disruption
Poor	Significant barriers, waste, frustration, inconsistency (etc.) in finding what is needed on demand	Issues which require resources (time, people, etc.) to resolve or not optimally support QRA / RBDM

Figure 4 - Rubric to support knowledge mapping

With these instructions defined, the assessment can continue on a line-by-line basis, for each of the 57 knowledge sources previously defined. It is good practice to split knowledge sources into each explicit and tacit rows where appropriate. Following this process for each of the 57 knowledge sources, a knowledge map can be created as illustrated in Figure 5, using the example of *History of problems with process/outputs*. Additional data can be collected at the discretion of the assessment team, such as where the knowledge is currently stored, who the subject matter expert (SME) is, etc.

Knowledge Input to QRA	**Tacit or Explicit**	***FLOW*** **of knowledge** - **Available, accessable, on demand**? - Are **heroics** needed? - A **newcomer** figure it out quickly?	***QUALITY*** **of knowledge** - **Reliable** (for intended use)? - Sufficient **Context & Rationale**? - Is it **Complete & Accurate**?	**Comment / Explanation**
example **History of Problems with process/outputs**	Explicit	Marginal	Marginal	No standard repository in use across multiple sites using the same equipment makes it difficult to find documents
	Tacit	Poor	Excellent	Difficult to know who SMEs are at various sites - and the SME at the vendor is always traveling so is difficult to talk to - but once we find the right people we get what we need

Figure 5 - Sample knowledge map (assessment of flow *and* quality*)*

While the knowledge sources may well be fairly consistent across organizations, the results of the knowledge map assessment are likely to vary by organization. Well-defined GMP documentation should always be straightforward to find while tacit knowledge (e.g., lessons from the past or similar products) can often be a challenge. Many other factors can come

into play, such as the size, complexity and distribution of the organization, age of products and technologies (extremely old and extremely new knowledge may be more challenging), prior efforts in creating platform knowledge, extent of standardisation of how IT tools are used, work done by third parties, and many more.

Step 4: Evaluate and prioritise opportunities for improvement

With the knowledge map populated, problem areas can be identified by using the knowledge map as a 'heat map' to explore the areas that received the lowest ratings. At this point, potential actions or solutions can be defined as illustrated in the example provided in Figure 6, which identifies problems and potential solutions for both explicit knowledge flow and quality, and tacit knowledge flow.

Knowledge Input to QRA	Tacit or Explicit	*FLOW* of knowledge	*QUALITY* of knowledge	Comment / Explanation	Possible Solution
example **History of Problems with process/outputs**	Explicit	Marginal	Marginal	No standard repository in use across multiple sites using the same equipment makes it difficult to find documents	- short term: create a list of repositires used and ensure they are used consistently; - long term: standardize, or at least reduce the number of repositories in use
	Tacit	Poor	Excellent	Difficult to know who SMEs are at various sites - and the SME at the vendor is always traveling so is difficult to talk to - but once we find the right people we get what we need	- Create a SME list - Ensure the right support in place from the vendor with alternate SMEs or urgent access

Figure 6 - Potential solutions for knowledge flow / quality gaps

A good practice would next be to employ a means of prioritisation to identify where to focus first, once all of the problem areas have been identified.

While the assessment of knowledge flow and quality during knowledge mapping is highly qualitative, very simple solutions to enhance knowledge flow and quality can emerge – such as increasing the awareness of where knowledge is currently stored through training, granting system access to a group 'not in the know', creating a simple list of SMEs, etc. More complex solutions might involve establishing a lessons learned process, establishing communities of practice, defining and maintaining domains of platform knowledge (i.e., often cited as an example of 'prior knowledge') and other knowledge transfer and capture approaches.

Conclusion and Next Steps

There are well-defined requirements for sources of knowledge to be used to inform risk assessments, of which this paper has started to catalogue. While the case study herein focused on a C&Q scenario, the authors expect many of these knowledge sources to be broadly applicable to other QRAs. Once solutions are in place for any knowledge flow or knowledge quality gaps – those issues are likely to be addressed for all processes – not just C&Q. Regardless of the area, the process is the same: understand the scope of the risk assessment, holistically define what knowledge should inform the best possible risk assessment, create a knowledge map to assess the knowledge flow and quality. The

knowledge mapping process and ensuing solutions do not need to be elaborate to have an impact. Furthermore, having these knowledge sources well understood will almost certainly benefit risk communication, risk review, and ultimately, risk-based decision making.

Exploration of these topics to operationalize the *RKI Cycle* are ongoing, including a planned ISPE *Expert Xchange* in 2022 to engage with industry on the knowledge mapping process for node 1 of the *RKI Cycle*, with a paper anticipated by late 2022 to report the results.

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