Knowledge as the Currency of Managing Risk: A Novel Framework to Unite Quality Risk Management and Knowledge Management

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Abstract

In a manner of speaking, *knowledge is the currency of managing risk* and an organization that is risk-focused will want to apply the best of what it knows to assess those risks, identify appropriate risk controls and evaluate the performance of those controls. An organization that effectively manages knowledge should be able to recognize and proactively apply new learnings to better anticipate risks. This is particularly important in the manufacture of medicinal products. Since the publication of ICH Q10 in 2010, QRM and KM have been positioned as co-enablers to the Pharmaceutical Quality System. However, in practice these two disciplines have remained largely distinct and disconnected. This paper presents a novel way to consider Quality Risk Management (QRM) and Knowledge Management (KM) which represents their true interdependencies, and which has the potential to deliver more effective and risk-based control strategies in a more synergistic and effective manner. This paper advocates for the need to strengthen the relationship between QRM and KM. In order to better understand the synergistic relationship between QRM and KM, a *Knowledge Management process model* is first proposed to envision KM akin to the familiar representation of QRM in ICH Q9 . Following this model, a framework is presented in the form of a *Risk-Knowledge Infinity Cycle* which serves to visualise and understand the QRM-KM relationship. It is the authors belief that treating QRM and KM in this way has a variety of potential benefits for biopharmaceutical companies, including improved risk-based decision making, facilitating evidence-based risk reduction and increased process knowledge, leading to less uncertainty and subjectivity in QRM outputs. This should ultimately result in more effective risk-based control strategies and more reliable manufacturing processes, which potentially lead to increased protection – and other benefits including product availability and value – for patients.

1. Introduction

In a recent paper by the authors, the relationship between risk management and knowledge management was explored, both in the biopharmaceutical industry and other sectors. Furthermore, the regulatory guidance which applies to the management of risk and knowledge within the biopharmaceutical industry was examined [1]. The paper, which included a detailed literature review of the subject matter, made the case that "risk varies inversely with knowledge application" and suggested that the relationship between quality risk management and knowledge management in the biopharmaceutical industry should be further examined as a first step to better connecting the dual enablers of the Pharmaceutical Quality System (PQS), Quality Risk Management and Knowledge Management, as presented in ICH Q10 [2]. The earlier paper further established that knowledge is both an *input to* and an *output from* risk management activities, and that quality risk management and knowledge management are how risk and knowledge, respectively, are systematically 'managed'. This concept of linking quality risk management and knowledge management has been proposed at a high level by others, including Calnan, who asserted "in many organizations, QRM and KM operate, at best, in parallel and are neither well integrated nor well balanced" [3]. Calnan went on to propose the need for a balanced integration of the two ICH Q10 enablers. However, arguably, the most familiar description and representation of the quality risk management and knowledge management relationship flows from ICH Q10 [2] where the two enablers appear adjacent to each other, but not connected (Figure 1). Recent observations at regulatory-focused conferences have acknowledged the disparity between progress in the two disciplines [4], and the fact that there is a lack of evidence on meaningful progress to better connect the two.

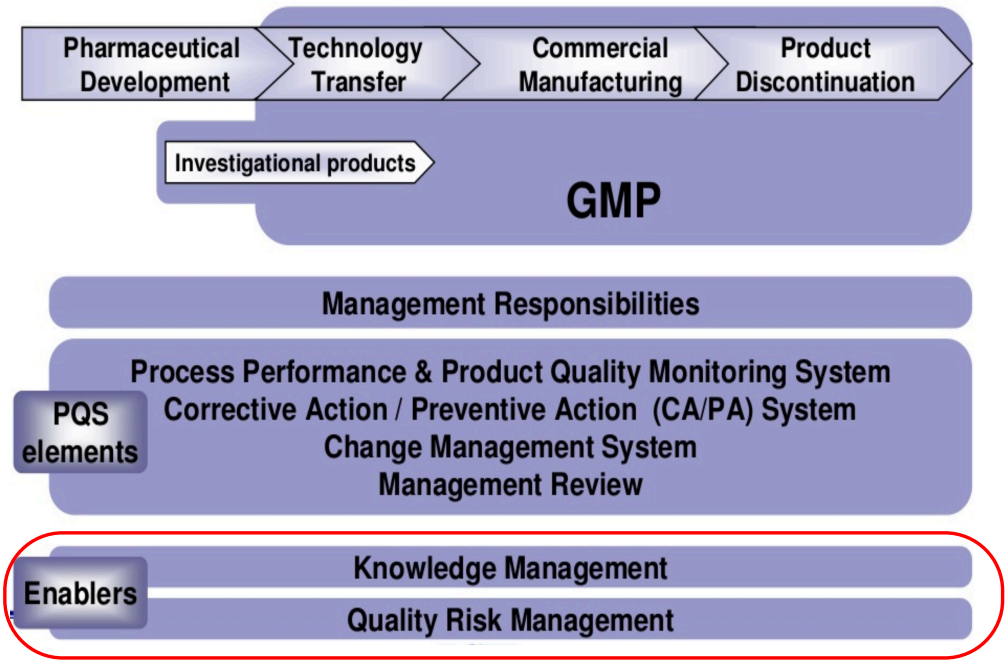

Figure 1 – KM and QRM as adjacent but disconnected enablers of the Pharmaceutical Quality System (ICH Q10) [2]

This paper further describes and strengthens the link between QRM and KM, proposes a *Knowledge Management process model* akin to the QRM process model in ICH Q9 [5] and presents a novel framework in the form of a *Risk-Knowledge Infinity Cycle* which serves to visualise and understand the QRM-KM relationship.

2. Back to Intent: Revisiting the Goals of Quality Risk Management & Knowledge Management

ICH Q10 [2] clearly identified Quality Risk Management (QRM) and Knowledge Management (KM) as enablers to an effective Pharmaceutical Quality System, however their interrelationship was never defined nor explored to any depth. Table I provides a brief outline of the independent goals of each QRM and KM.

Table I – Goals of each QRM and KM

Quality Risk Management

According to ICH Q9 [5], "Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

[The] two primary principles of quality risk management are:

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

ICH Q9 also provides the familiar and often cited visualization of the QRM process (Figure 2) [5].

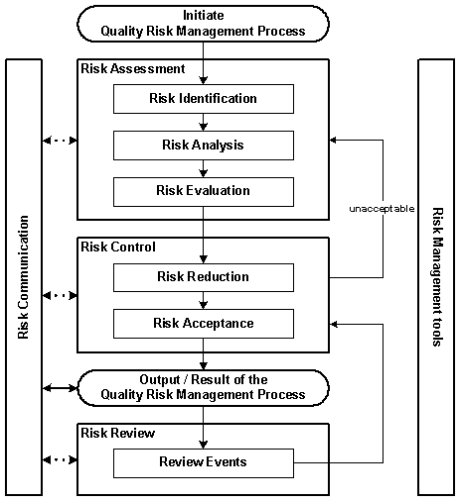

Figure 2 – QRM Process [5]

In summary, the purpose of QRM is to reduce risk to the patient (through managing risk to quality across the product lifecycle), based on applying the scientific knowledge available in the organization.

Knowledge Management

According to ICH Q10 [2], KM is defined as a "systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components."

The ISO standard on KM, *Knowledge Management Systems – Requirements ISO 30401:2018* [6] defines KM as "Management with regard to knowledge," noting (a) It uses a systemic and holistic approach to improve results and learning, and (b) It includes optimizing the identification, creation, analysis, representation, distribution and application of knowledge to create organizational value.

Another description of KM is shared by Martin who states "a key goal of KM is to deliver the 'right' or best available information, to the right person, at the right time, to make the right decision and/or give the right advice" [7]. This is consistent with the advice of other experts in KM, such as APQC, who also characterize KM to be about enabling knowledge to "flow" [8].

In summary, the purpose of KM is to ensure that knowledge is readily available to drive informed decision making through a systematic and holistic approach including acquiring, curating (capturing, identifying, reviewing and analysing), disseminating (including knowledge visibility and availability) and applying knowledge.

Given the goals of QRM and KM, it would seem intuitive that risk assessment and QRM activities should be based on the best available knowledge, and that whatever approach to KM is adopted, it should be systematic and designed such that it provides the relevant knowledge to the right people, at the right time. An effective approach to KM should improve QRM, serving to further reduce risk to the patient, as the *lesser* the knowledge, the *higher* level of uncertainty and unknowns, and therefore the *higher potential risks* to product quality and/or patient safety [9]. Systematic KM can support having optimum controls in place which are not only a response to the potential risks in that part of the process, but also are based on the collective knowledge available on that process and product within the organization, including prior knowledge from other products and platforms. *Not* leveraging a holistic body of knowledge in this way during QRM activities can introduce selectivity and subjectivity which may result in possible hazards occurring which could have an impact on product quality and on patients.

3. Knowledge Management to Enhance Quality Risk Management Outcomes

The practice of KM presents a diverse and adaptive set of practices to enhance knowledge flow and application. A well-designed, holistic and systematic KM program will strengthen QRM through the availability of critical knowledge, including product knowledge, process knowledge, platform knowledge and other relevant knowledge. Such a KM program can support the curation, sharing and dissemination of knowledge which can subsequently be applied and transferred to inform decisions and achieve other objectives. Typically this knowledge resides in documents housed in repositories, within communities, lessons learned, best practices, experiences and expertise. This can also include knowledge from other products, other sites, other modalities, as well as knowledge from past changes, from prior risk assessments, and a wide variety of other sources. A *Knowledge Management process model* which illustrates the role of KM in how an organization can manage its knowledge as an asset is proposed [10] by the authors and is presented here in Figure 3. This model can be viewed as a KM analogue to the QRM process model presented in ICH Q9.

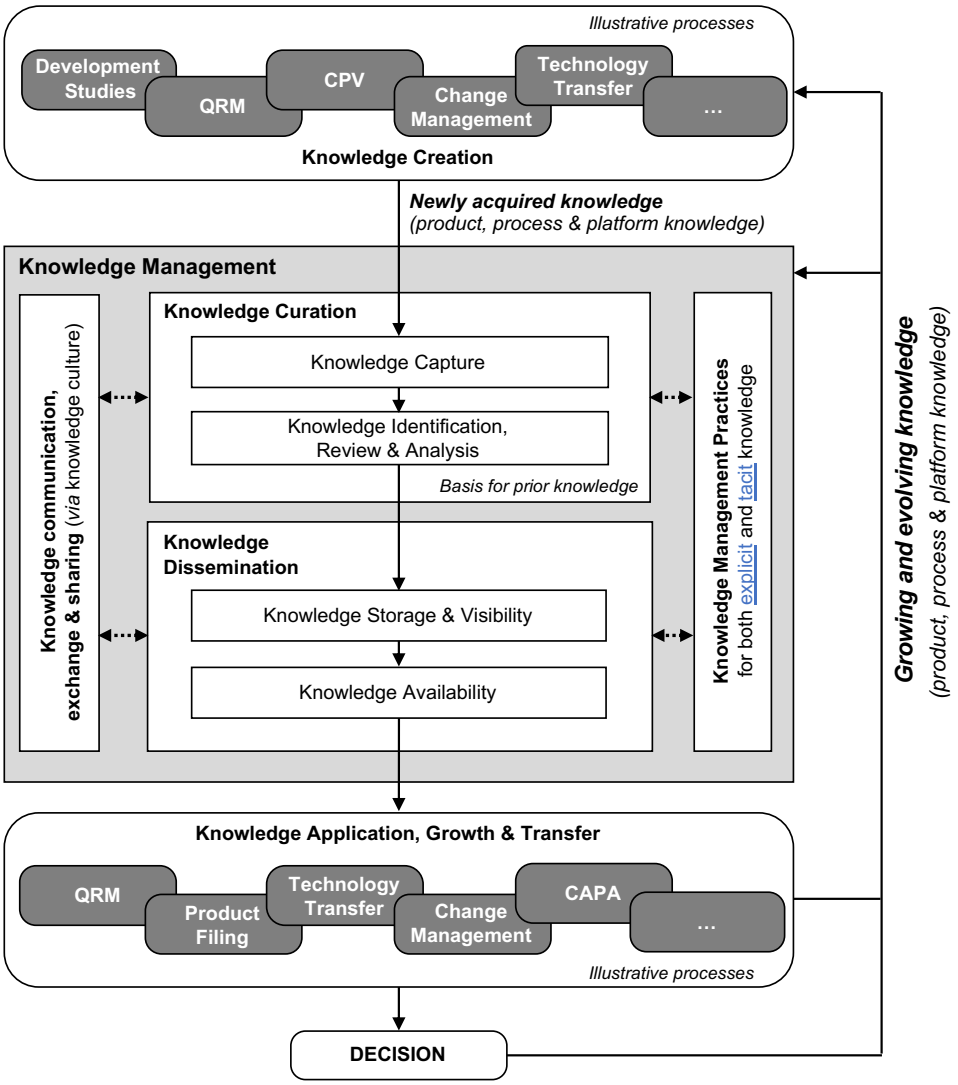

Figure 3 – Knowledge Management process model [10]

This process model (Figure 3) features traceability to the definition of knowledge management in ICH Q10 (i.e. "systematic approach to *acquiring*, *analysing*, *storing*, and *disseminating* information…", see Table I). Each of these activities defined in ICH Q10 is represented in the model. In the opinion of the authors, this process model further enhances the ICH Q10 definition through additional context, details and mapping of interactions within the model. Consider the following features of the model:

(i) Knowledge is **acquired (created) through a variety of important processes and activities**. This knowledge must flow into the knowledge management construct to be 'managed' (i.e. to be systematically curated, shared and disseminated for future use).

(ii) The overall process of knowledge management is divided into two main activities. A phase for ***knowledge curation***, where knowledge is intentionally *captured* and subsequently *identified*, *reviewed* and *analysed* as appropriate. Curation is defined as "*the action or process of selecting, organizing, and looking after the items in a collection"* [11]. This activity involves proactively stewarding and caring for the knowledge assets of the organization to ensure they are available and suitable for use when needed. The second phase is ***knowledge dissemination***, where the importance of not only knowledge *storage* but also *visibility* and *availability* (inclusive of accessibility) are highlighted. Of note, *Knowledge dissemination* may be on a 'pull' and/or a 'push' basis, meaning it can be 'pulled' on demand by a process (e.g. obtain specifications for technology transfer) or it can be 'pushed' to those that need to know (e.g. sharing a lesson via a community or by building into a business process).

(iii) The 'how' for these two major activities is accomplished through **KM practices**. Practices should be employed for both explicit knowledge (e.g. content management, taxonomies, search) and tacit knowledge (e.g. communities of practice, expertise location, lessons learned). These KM practices are best supported by a series of enablers (e.g. standardized processes, sponsorship and training) [12].

(iv) **Knowledge communication, exchange and sharing** represents the sharing of knowledge and learning based on the mindsets and behaviours of an effective knowledge culture [13], where people can ask questions, learn from each other and make connections to learn and grow their individual knowledge and collectively that of the organization.

(v) **Knowledge is applied** to a variety of important processes and activities. Knowledge is an indispensable asset which powers a variety of critical processes and enables the **best possible DECISION** (or other desired process outcome) for QRM and many other processes.

(vi) A **feedback loop** is included for the growth and evolution of knowledge which provides an input to future processes and also grows the knowledge base of the organization.

One can envision the benefit to improved understanding and decreased uncertainty by "unlocking" the knowledge of the organization as depicted in Figure 3, as well as to many other benefits of knowledge access and availability for resolving investigations, post-approval changes and more. It is the discipline of Knowledge Management to make this into a reality.

In the opinion of the authors and further supported by an absence of evidence in relevant literature, it is unlikely that QRM today routinely leverages the best knowledge an organization has to offer. Certainly, one contributing factor is the relatively low maturity of KM programs in the biopharmaceutical industry [4, 14]. Yet, as established in a previous examination relating QRM and KM [1], there is a strong interdependency between knowledge and risk. In a manner of speaking, *knowledge is the currency of managing risk.* Recognizing this, there is an opportunity for organizations to better leverage their KM practices and programs as a means to improve risk reduction (or to define and deploy KM practices and programs if they don't exist).

4. Re-imagining the Quality Risk Management – Knowledge Management Interdependency

Reflecting on the insights gained in the course of this research on each risk, risk management, knowledge and knowledge management, including:

- Risk varies inversely with knowledge, perhaps more accurately risk varies inversely with knowledge application, suggesting the knowledge has to be available and actively used in the reduction of risk; Given the overarching goal of risk management is to *minimize* risk, this relationship suggests one should maximize knowledge and its application to inform risk;
- Knowledge is both an *input* and an *output* to the risk management process which in turn informs risk – essentially knowledge weaves in and out of the various activities within the risk management process;
- KM is about knowledge flow and ultimately knowledge application;
- QRM can enable the best outcomes and further reduce risk to patients by leveraging the best available knowledge about products, processes and platforms, including prior knowledge;
- QRM is a discrete event in applying knowledge to inform decisions.

Together, these insights suggest an underlying interdependent relationship between risk and knowledge. The authors reflected on what this might mean in practice. In reflection, how does KM maximize knowledge availability and enable this knowledge to flow through QRM to in turn reduce risk? Furthermore – for the knowledge outputs from the QRM process (e.g. risk assessments, decision criteria, adequacy of risk controls, identification of "known-unknowns" (i.e. knowledge gaps to address)) – how does this knowledge flow and become managed through KM practices for future use or use by others? For example, how does the knowledge gained from each knowledge management and risk management inform and improve the control strategy?

In response, the authors propose a simple framework, the *Risk-Knowledge Infinity Cycle* [10], as a visualization of how risk and knowledge are connected, presented here in Figure 4.

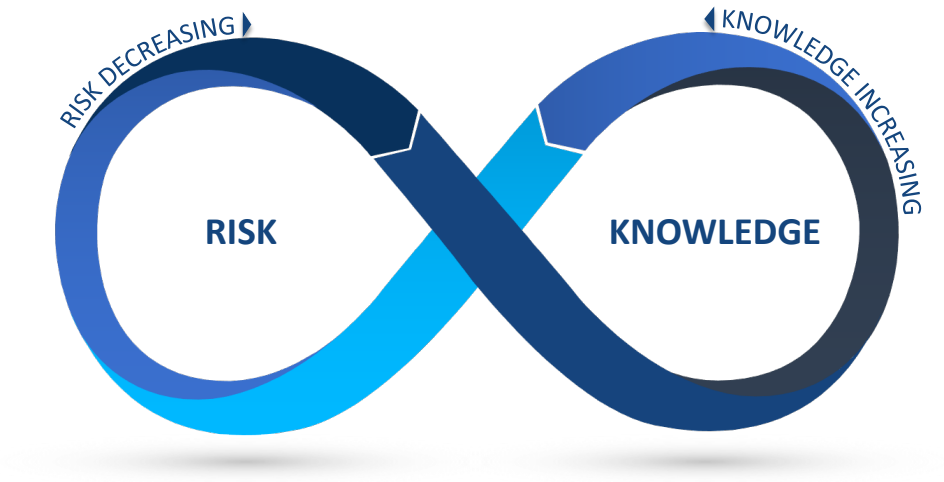

Figure 4 – The Risk-Knowledge Infinity Cycle [10]

The key features of this *Risk-Knowledge Infinity Cycle* include:

(i) The **interwoven relationship** between knowledge and risk, where knowledge feeds in to inform risk, and risk informs what is known, including the need to acquire new knowledge…*knowledge and risk inform each other.*

(ii) The **inverse relationship** previously established [1, 9], where increased knowledge leads to decreased uncertainty and decreased risk. Figure 5 below provides a visualisation of this concept over time for a product. In the early stages of a product's lifecycle, risk is *high* since knowledge is *low*. Risk can be immediately reduced through the application of prior knowledge. Risk is further reduced through increasing and applying knowledge by other means, including development activities, manufacturing experience and risk review. A well-characterized product for which there is an abundance of knowledge will result in lower risk.

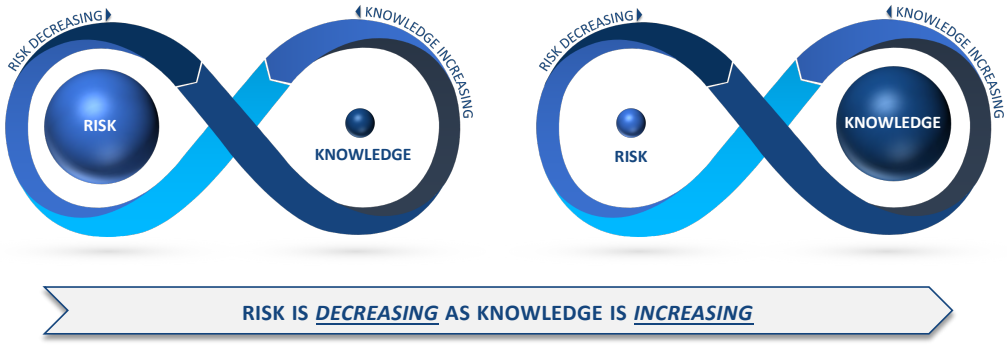

Figure 5 – Decreasing Risk Through Increasing Knowledge [10]

(iii) The **concept of flow** – that knowledge should *flow* effortlessly to inform risk, and likewise, risk seamlessly informs knowledge and gaps in knowledge (i.e. 'known-unknowns').

(iv) The cycle is **continuous and perpetual**, as suggested by the use of the infinity symbol and infinity appearing in the framework title. Knowledge is always evolving and should be applied to inform risk (even if reaffirms what is already known to grow confidence in risk controls), and one will always learn about new risks and the performance of risk controls, thus generating *both* new knowledge and the need for new knowledge.

To illustrate this framework in practice the authors applied [10] the *Risk-Knowledge Infinity Cycle* to ICH Q10 to help demonstrate the interaction between QRM and KM. This application to ICH Q10 is depicted in Figure 6.

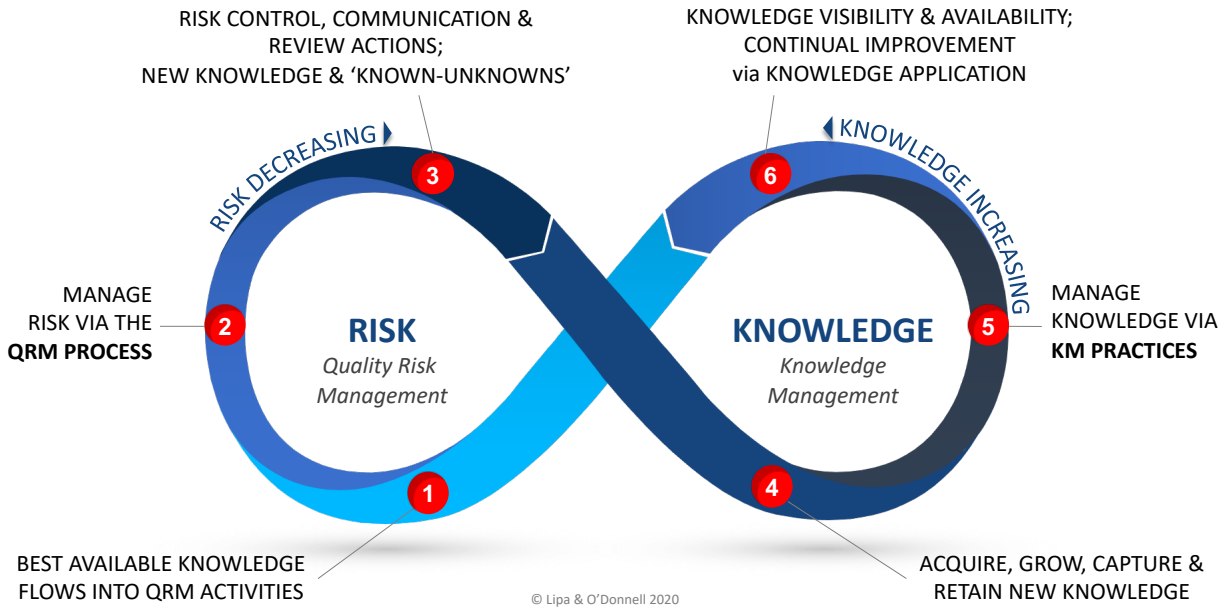

Figure 6 – The Risk-Knowledge Infinity Cycle applied to ICH Q10 [10]

In this case, QRM and KM are interdependent and in unison enabling the Pharmaceutical Quality System. The application of the two ICH Q10 co-enablers are not distinct but are in fact interwoven with each other – knowledge informing quality risk – quality risk creating knowledge – knowledge informing quality risk…and so on. This is consistent with research in integrating risk and knowledge management in human spaceflight programs by Lengyel [15]. Lengyel asserts "risk management and knowledge management have been shown to exhibit a reciprocal relationship. Risk management identifies knowledge gaps and knowledge management is a means of identifying resources to fill those gaps."

Among the key benefits of the *Risk-Knowledge Infinity Cycle* framework applied to ICH Q10 include:

(i) The recognition of QRM and KM being separate, distinct disciplines yet interdependent on each other for ultimately reducing risk to patients

(ii) This cycle can repeat for each phase of the QRM cycle, including when new knowledge is acquired, and with each pass through the cycle, knowledge is increased while risk is decreased

(iii) Consistent with the underlying framework, the interwoven relationship between knowledge and risk (and knowledge management and risk management), the inverse relationship of increasing knowledge leading to decreased risk, the concept of flow, and the continuous and perpetual cycle are each relevant to the goals of the PQS.

In addition, Figure 6 depicts six steps in the in the cycle illustrated as nodes labelled 1 through 6. They are intended to highlight key activities of the interaction between QRM and KM. Table II provides further detail on each of these six steps.

Table II – Six steps in the Risk-Knowledge Infinity Cycle framework (starting at number 1 and proceeding counter-clockwise around numerically to number 6)

	Stage	Description
QRM domain	**Stage 1** Best Available Knowledge Flows into QRM Activities	***Best available knowledge flows easily into QRM***, including (but not limited to) *prior knowledge, product, process and platform knowledge*, and any other relevant knowledge (e.g. supply chain, regulatory, facility knowledge, et al.).
	Stage 2 Manage Risk via the QRM Process	A robust ***QRM process reduces risk to quality*** through methodical Risk Assessment, Risk Control, Risk Communication & Risk Review Quality risk reduction benefits from applying the collective knowledge of the organization across the range of QRM phases providing the best perspectives, historical experience and learnings and best practices on what could happen and how it can be most effectively controlled.
	Stage 3 Risk, Control, Communication & Review Actions; New Knowledge & 'Known-Unknowns'	***Outputs from the QRM process constitute new knowledge***, including new decisions (with associated context and rationale), risk control plans, recognized gaps in knowledge ("known-unknowns"), lessons learned, communication requirements and essentially become 'prior knowledge' for future risk management.
KM domain	**Stage 4** Acquire, Grow, Capture & Retain Knowledge	***Grow and Retain the body of knowledge.*** New knowledge and experience are acquired through a variety of means, whether intentional studies to close knowledge gaps identified during QRM, technology transfer, continual improvement, investigations, planned changes and accumulated manufacturing experience. This new knowledge must be proactively managed – including explicit knowledge (typically documents) as well as a means to surface and capture tacit knowledge (knowledge in the heads of people) through capturing lessons learned and best practices, engaging in communities of practice, etc.
	Stage 5 Manage Knowledge via KM Practices	***Knowledge is managed as an asset through an appropriate set of KM Practices*** which deploys a variety of KM practices to facilitate the curation, sharing and flow of both explicit and tacit knowledge; These practices are inclusive of the facets of people and culture, process, technology and governance to ensure the best outcomes and sustainability.
	Stage 6 Knowledge Visibility & Availability; Continual Improvement via Knowledge Application	***Knowledge visibility, availability and transfer leads to continual improvement*** via a variety of means including controlling risks, identifying new best practices, implementing lessons to ensure issues are not repeated (and good practices are captured).

Table III is an illustrative example of a quality risk assessment for a sterile filling line, and the corresponding details for each of the six key steps identified in the *Risk-Knowledge Infinity Cycle*.

Table III – Practical Application of the Risk-Knowledge Infinity Cycle - example for a sterile filling line risk assessment

	Stage	Example – Sterile Filling Line QRA
QRM domain	**Stage 1** Best Available Knowledge Flows into QRM Activities	Useful sources of knowledge include the following and they should be used: • Design documents, specifications and drawings • Supplier documentation (complaints, investigations & follow up) • Filling Non-conformances / deviations and CAPA follow up • Product complaints indicating sterility assurance concerns / CAPA follow up • Trend analyses of all monitoring and testing • Audit results and follow up • Procedures and warnings / alerts • Prior risk analyses performed with supporting rationale • Process simulation (media-fill) results • Environmental monitoring results • Subject Matter Experts in product, process, platform • Hazard libraries related to sterility assurance (which represent accumulated lists of potential risks for a given situation) • Relevant knowledge from other manufacturing sites or similar products, including any lessons learned on product, process or equipment • Performance of prior risk controls contributing to sterility assurance
	Stage 2 Manage Risk via the QRM Process	• A QRM plan is in place • QRM roles have been established • Sufficient QRM competency exists • A QRM community is in place (where there is support for the QRM process and connectivity of QRM practitioners) • Risk communication mechanisms are in place

	Stage 3
	Risk Control, Communication & Review Actions; New Knowledge & 'Known-Unknowns'
		• Decisions in relation to risk controls are documented and captured
		• Residual risks are estimated with supporting rationales captured
		• Risk control actions are defined and deployed, e.g.
		  ○ New studies are performed to identify the required risk controls (e.g. addressing a 'known-unknown')
		  ○ Required SMEs (subject matter experts) and/or CoEs (centers of excellence) are engaged (e.g. glass breakage team)
		  ○ Risk mitigating procedures are put in place (e.g. for filling equipment set up, for cleaning)
		  ○ Risk mitigating training procedures are put in place (e.g. for gowning, aseptic connections and interventions)
		  ○ Fault tree analyses are performed to determine interactions between causes that can lead to failure and to identify new risk controls
		  ○ Risk mitigating equipment changes are made (e.g. addition of monitoring sensors on the filling line)
		• Risk communication is initiated to appropriate stakeholders
		• Risk review is planned and initiated

Table III continued

	Stage	Example – Sterile Filling Line QRA *(continued)*
KM domain	**Stage 4** Acquire, Grow, Capture & Retain Knowledge	This involves the following: • Appropriately managing knowledge assets from Stage 3 • Capturing knowledge about the performance of risk controls • Acquiring knowledge from new studies • Acquiring knowledge from change activities • Acquiring knowledge from investigations • Acquiring related knowledge from adjacencies – e.g. the same product at other facilities, other products on the same line, etc. • Acquiring knowledge from transfers, in or out • Accumulating the experience gained over time
	Stage 5 Manage Knowledge via KM Practices	• A KM plan is in place for site/department(s) • KM roles are established • Systematic KM standard practices exist and are in use • KM competencies exist for all staff involved in risk assessments and QRM activities • Mindsets and behaviours to manage knowledge as an asset are demonstrated • KM reporting systems are in place

	Stage 6
	Knowledge Visibility & Availability; Continual Improvement via Knowledge Application
		• A comprehensive body of knowledge for a given product / process / platform is compiled (e.g. knowledge is extracted from the sources specified in Stage 1), and this knowledge may be used to:
		  ○ support process, product and other changes
		  ○ resolve investigations more quickly
		  ○ support continual improvement
		• Knowledge is acquired and managed to inform decisions
		• Knowledge is acquired for quality risk management

5. Potential Benefits of Quality Risk Management and Knowledge Management as United ICH Q10 Enablers

ICH Q10 [2] depicts QRM and KM as dual, but not expressly united, enablers to the PQS (Figure 1). In contrast, per the arguments presented in this paper the authors envision the twin PQS enablers can be re-framed in a united fashion as depicted in Figure 7.

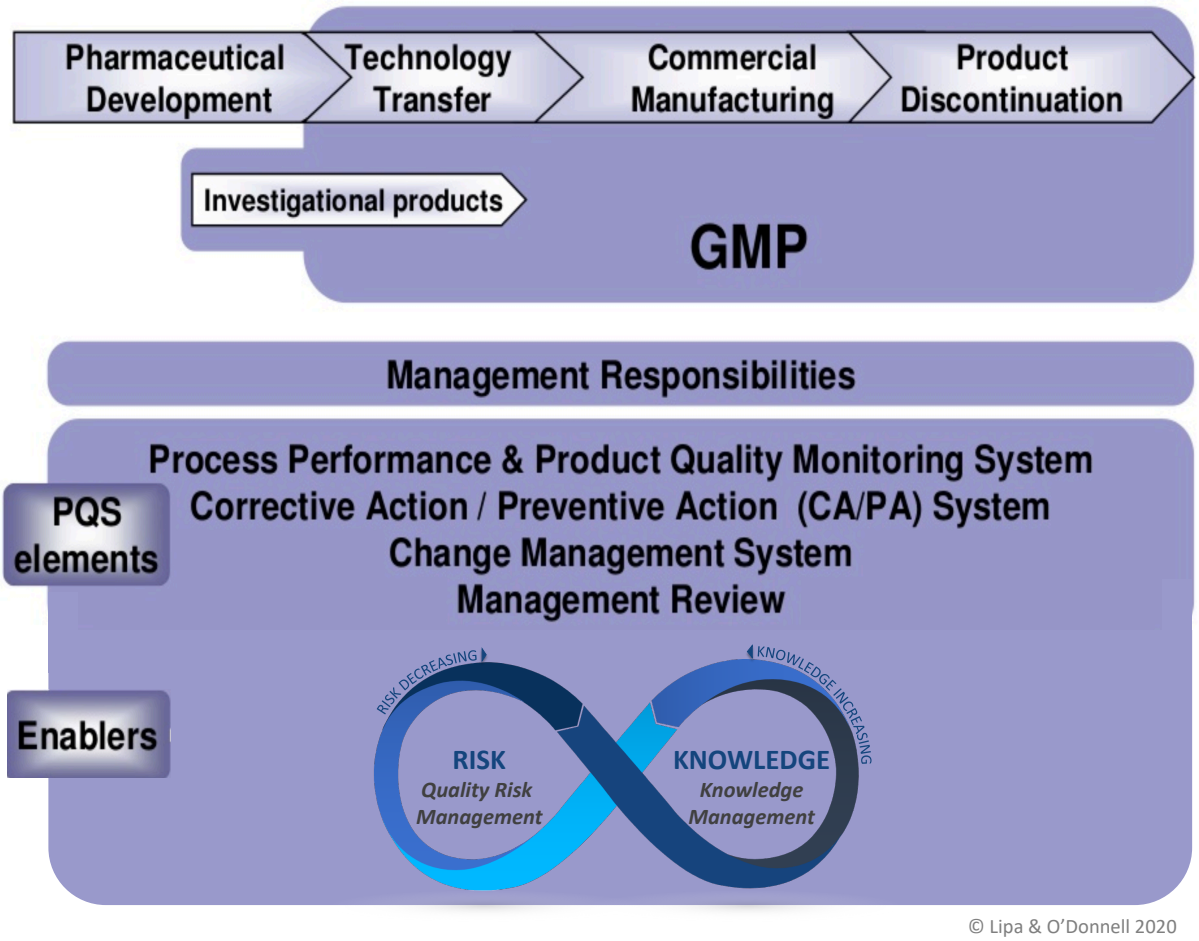

Figure 7 – A Re-framed and United PQS foundation [10]

In this case, QRM and KM are positioned as being interwoven and are directly linked to enabling the four PQS elements of *Process Performance & Product Quality Monitoring System*, *Corrective Action / Preventative Action System*, *Change Management System* and *Management Review*. Further elaboration on specific linkages for each of these PQS elements will be the subject of future papers, but at a high level, there are several benefits to be gained by designing one's PQS where QRM and KM are directly linked and interwoven. Some of these potential benefits are as follows:

- **Achieving true risk-based control strategies:** Risk assessments that are informed by the knowledge of which GMP controls are truly important in controlling risk should result in

control strategies and their associated equipment qualification / process validation protocols that are truly risk-based and value-adding. This link between knowledge and risk assessment is fundamental, and it requires an approach to KM that enables all risk assessments to access and make use of such knowledge. This kind of approach should ultimately result in increased levels of patient protection, via control strategies and qualification / validation activities that truly address risk. Annex 15 to the EU GMP Guide [16] supports the concept of understanding the importance of the various GMP controls from a risk control perspective; it states that "Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities."

- **Evidence-based Risk Reduction:** A knowledge of which GMP controls are truly important in controlling risk should also lead to more evidence-based risk reduction, whereby the level of risk reduction that is delivered by a set of GMP controls in a process can be measured (or at least estimated with a high degree of confidence). This is of benefit, because the ability to measure or estimate the risk reduction delivered by, or expected from, risk control activities should enable companies to demonstrate increased levels of process understanding and process knowledge. It should also help decision makers make more informed decisions on the outputs of QRM activities, i.e. whether the suggested risk control strategy will lead to the degree of risk reduction that is expected. This link between knowledge and risk control is also fundamental, and it requires an approach to KM that facilitates the application of knowledge about GMP controls and manufacturing processes during risk control activities.

- **Increased knowledge leading to less uncertainty and subjectivity in QRM outputs:** Risk assessments and risk ratings that are based on scientific data as well as process, equipment and material knowledge will be inherently less subjective and uncertain in their outputs. Such risk assessments are informed not only by the GMP controls that are, or are not, in place, they are also informed by a knowledge of the true effectiveness of those controls. In this regard, any probability of occurrence ratings that are assigned to hazards or failure modes are based on a formal assessment of the preventative nature of those controls. Severity ratings that are assigned to the effects of hazards or failure modes are based on a formal assessment of the controls that may reduce those severities, should the hazards or failure modes occur, and detection ratings are based on a formal assessment of the known or likely effectiveness of the various detection controls that are cited in the risk assessment. In addition, in such risk assessments all GMP controls that are considered important in risk control are formally assessed for their qualification or validation requirements. Such an approach to KM and QRM is beneficial, because it delivers QRM outputs that are based on GMP controls and knowledge rather than on guesswork, uninformed opinions and highly subjective risk ratings. It should deliver more reliable estimates of risk, as well as practical ways to estimate (or measure) risk reduction and residual risk. It should also benefit companies through having fewer inspectional issues in areas directly related to risk estimates, e.g. deviations and change control, supplier and CMO oversight, etc.

There are other advantages to be gained via stronger linkages between QRM and KM. For example, managing the knowledge pertaining to the various GMP controls in a manufacturing process can enable a company to reflect in subsequent risk assessments and estimate how much prevention (as opposed to detection) has been built into the control strategy. This kind of analysis is useful, as it enables one to assess the extent of proactive prevention vs. reactive detection in a process and its control strategy, and that information is very useful. Doing this can inform not only risk review activities for that process, but also future risk assessments that might be performed on the process. In fact, during every risk assessment, it is probably beneficial to estimate the ratio of prevention vs. detection in the overall set of risk controls for that process or unit operation, as this information tells a lot about the nature of the risk control strategy.

Another example of an advantage to using this linked approach between QRM and KM relates to demonstrating PQS effectiveness. What if a company managed knowledge about its change control activities in such a way that it could show on an annual basis how much of its change control activities for the previous year *led to risk reduction and continual improvement?* Would that be an attractive target condition to aim for? Or, if its Annual Product Review (APR) / Product Quality Review (PQR) process supported advanced risk review activities, whereby the APRs/PQRs serve as *a formal tool for communicating knowledge about the residual risk levels in the concerned process?* This might be what a truly effective PQS looks like! QRM & KM together can help achieve both of these scenarios, if done correctly!

One final example relates to decision-making. Much of GMP is about risk-based decision making, be it in relation to deviations and other investigations, the adequacy of a validation protocol, the outcome of a supplier assessment exercise, etc. Risk-based decision making requires lots of things…it requires a culture that proactively supports decision-making based on fact, science, considered thinking, experience, expertise, knowledge, risks and benefits, etc. It also requires systems that collect and convert data, information and learnings into ready-to-use knowledge. So it is useful to ask, how does the PQS that we work within enable the capture and maintenance of new knowledge? What aspects of our PQS make this happen? Can we demonstrate that our PQS is actually doing this? It is helpful if there are standardized repositories for GXP and non-GXP technical product and process knowledge in place, as we need an ability to quickly connect and apply the experience and expertise within the organization (tacit knowledge / know-how). Risk-based decision making is also facilitated by having formal Lessons Learned systems in place, including for near misses (and not just for deviations, tech transfer issues, etc.)

The potential benefits associated with such KM systems that support risk-based decision making are numerous. First and foremost, there can be increased protection and value for patients – via the decisions reached that resulted in consistently high quality and available medicines for patients. There can also be an increased r*eturn-on-investment* for companies, where better decisions lead to more efficient operations and lower costs, and less chances of serious manufacturing problems and non-compliances occurring. In addition, if a company can show its regulators that it has a good handle on capturing and leveraging prior knowledge, this should

give regulators increased confidence to support increased flexibility for the site, and it may also lead to Q12 realization – in relation to flexibility for post-approval changes (PACs).

Several of the above areas could benefit from further research work. For example, controlling subjectivity and uncertainty in the outputs of QRM activities is an area that is quite under-developed at this time within the GMP environment. Additional effort is needed to better understand how the effects of biases and cognitive heuristics can be counteracted when assessing risks, especially when assigning probability of occurrence ratings to hazards and failure modes. Further work is also needed to develop tools that can measure or reliably estimate the extent of risk reduction that is achieved via risk control activities. The crude estimations that are currently often performed are probably of limited value. In addition, the topic concerning risk-based decision making is one topic that could benefit from research, not least starting with understanding how other industries and disciplines have addressed this area and developed tools to support it.

6. Conclusion

As presented in this paper, there is a clear opportunity to explore, better define and strengthen the connection between QRM and KM. Knowledge can be seen as the currency for managing risk (and therefore the currency for quality risk management), and as established by logic and a detailed examination of the literature, increased knowledge can lead to decreased risk.

In the opinion of the authors, creating stronger ties between the two disciplines will be of mutual benefit to the respective disciplines. This might include ensuring that QRM processes at large influence the scope and focus of KM efforts, so those QRM processes are pre-positioned to use the best available knowledge for decision making. QRM tools and processes should be examined to ensure they are influenced by KM principles, such as how they capture tacit knowledge, how they identify experts for quality risk assessment activities and how they leverage prior knowledge from quality risk management activities and from the organization at large. The *Risk-Knowledge Infinity Cycle* framework presented above is one way to envision this relationship and it can be used by organizations to guide their thinking on how the disciplines of QRM and KM can be better connected in practical and tangible terms.

An organization that is always sensing risk will want to apply the best of what it knows to assess those risks, to identify appropriate risk controls and evaluate the performance of those controls. And an organization that is always managing knowledge will be able to recognize and proactively apply new learnings to better anticipate risks. These activities are “continuous and perpetual”, as proposed by the *Risk-Knowledge Infinity Cycle* framework, and they broadly impact all four of the key elements identified in the PQS.

It is important to note that the authors do not propose a convergence of QRM and KM into one singular ‘practice’. While synergistic and interdependent, the skills and focus of each discipline are distinct, as is ‘how and where’ the processes are deployed in the product lifecycle.

Converging the two would risk diluting the mission of each. In fact, the ISO standard on KM [6] summarizes a useful position on this, describing them as "parallel and complimentary", as follows:

> *"Knowledge management and risk management are closely linked in many ways, but remain separate disciplines. Although acquisition of effective knowledge management, … is one way to reduce or manage risk, there are other mechanisms than knowledge management for risk mitigation. Also knowledge management impacts business effectiveness, performance and reputation in ways other than risk reduction, such as capability enhancement or decision support.* ***Both knowledge management and risk management are disciplines for managing the intangible factors that affect the operation of an organization or project, and both need to be managed through the life of a project or as part of good organizational governance, but they should be seen as parallel and complementary rather than overlapping.****"*

Improving the connection between QRM and KM offers the potential for many significant benefits, including achieving true risk-based control strategies, evidence-based risk reduction and increased knowledge leading to less uncertainty and subjectivity in QRM outputs. A stronger connection between QRM and KM practices can also enable risk-based decision making on a variety of topics, potentially leading to increased protection for patients. Other potential benefits also exist, including an increased r*eturn-on-investment* for companies and increased confidence for regulators to support increased flexibility for the site and improved realization of ICH Q12 [17].

It is hoped that both the *Knowledge Management process model* and the *Risk-Knowledge Infinity Cycle* framework as presented in this paper will enable improved recognition of the interdependency between QRM and KM and empower organizations to take action to better connect the disciplines, leading to a variety of benefits as described herein.

Disclaimer

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