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Managing Knowledge and Risk: a Literature Review on the Interdependency of QRM and KM as ICH Q10 Enablers

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Abstract

Quality Risk Management (QRM) and Knowledge Management (KM) have been positioned as co-enablers to the Pharmaceutical Quality System since the 2010 issuance of ICH Q10. Yet these disciplines have remained largely distinct and disconnected in practice. This paper presents a two-part literature review on this topic. First is a review of how other industries have connected risk management and knowledge management. This is followed by a review of relevant biopharmaceutical industry regulatory guidance to explore expectations for how risk, risk management, knowledge and knowledge management are interdependent. The results suggest there is a strong argument in favor of linking risk management and knowledge management and other industries have demonstrated benefits in doing so. Furthermore, the review of the biopharmaceutical industry regulatory guidance shows the clear and persistent benefits of connecting the expectations of managing risk and knowledge together. A key conclusion is that risk varies inversely with knowledge application and therefore, a lower level of risk to quality (and ultimately to the patient) can be achieved through risk management practices when a thoughtful and programmatic approach to knowledge management is in place, providing the best possible knowledge to assess and control risk.
1 Introduction

In 2010, when ICH published Q10 *Pharmaceutical Quality System* [1], Quality Risk Management (QRM) and Knowledge Management (KM) were clearly identified as key enablers to supporting an effective Pharmaceutical Quality System (PQS). While the authors of ICH Q10 recognized the role both play in ensuring quality, they were identified as separate independent disciplines, and indeed in the main, this is how they are viewed in the Biopharmaceutical sector today, by both industry and regulators alike. Typically, quality risk management and knowledge management are described as mutually exclusive distinct management practices, each with their own programs, teams, training etc. Yet, one could argue that reducing risk via quality risk management is an exercise in knowledge, and applying knowledge via knowledge management is an exercise in reducing risk. Since 2005, the Pharmaceutical Regulatory Science Team (PRST) in Technology University Dublin (prst.ie) has been researching the disciplines of quality risk management and knowledge management and it is clear that a deep study into their interdependency is warranted. This paper explores their inter-relationship, and while acknowledging that each discipline has its own origins, it is suggested that there is an opportunity to strengthen the quality risk management and knowledge management relationship, with a clear benefit to patients.

Reflecting on the origins of ICH Q10, in August 2002, when the FDA announced the Pharmaceutical cGMPs for the 21st Century Initiative [2] it promoted “A science and risk-based approach to product quality regulation incorporating an integrated quality systems approach.” The emphasis then was on risk and science. On rereading this document 18 years later, one can’t help but notice the absence of the term “knowledge” in it. While the word ‘science’ is mentioned more than 15 times, ‘knowledge’ on the other hand is only mentioned once, and that is in a section called “science based policies and standards”. The FDA document suggested:

“Significant advances in the pharmaceutical sciences regulatory compliance in Regulatory Guidance and in manufacturing technologies have occurred in the last two decades. While this knowledge has been incorporated in an ongoing manner into FDA’s approach to product quality regulation, the fundamental nature of the changes dictates a thorough evaluation of the science...
base to ensure that product quality regulation not only incorporates up-to-date science, but also encourages further advances in technology. Recent science can also contribute significantly to assessment of risk.” [2]

In an article published in 2014 by PRST authors Greene and O’Donnell [3], it was suggested that the inherent relationship between science and knowledge cannot be disputed. Evidence of this was proven by various definitions of science as shown in Table I.

| Knowledge about or study of the natural world based on facts learned through experiments and observation | Merriam Webster Dictionary |
| A systematically organized body of knowledge on a particular subject | Oxford English Dictionary |
| Archaic knowledge of any kind | Oxford English Dictionary |
| A branch of knowledge or study dealing with a body of facts or truths systematically arranged and showing the operation of general laws | Dictionary.com |
| Systematic knowledge of physical or material world gained through observation and experimentation | Dictionary.com |
| Knowledge, as of facts or principles; knowledge gained by systematic study | Dictionary.com |

Table I - Definitions of Science

In the article Greene and O’Donnell suggest that:

’if we limit the knowledge we value to that which is aligned with science, which one could argue is truly “explicit knowledge,” one is ignoring a whole range of “tacit knowledge” spanning across the life cycle of the product’

In fact, to quote one of the most famous scientists of recent times, Albert Einstein;

“knowledge is experience, everything else is just information.”

Indeed one could ask: As the value of knowledge became more apparent since the publication of ICH Q10, has regulatory thinking emerged over the journey to recognize knowledge as the key, and science to be a subset of knowledge, rather than knowledge itself?

Turning now to quality risk management, it is important to note that the term ‘Quality Risk Management’ is typically a Biopharmaceutical Sector term, specifically as risk management directed at the management of risks pertaining to quality; other sectors and the literature tends
to use the generic term ‘Risk Management’ (RM), so for the purpose of this study, in particular when reviewing the literature, both QRM and RM are considered synonymous.

Indeed, a good place to start for any literature review is to provide definitions of the subjects under review; in this case, these are *risk*, *knowledge*, *risk management* and *knowledge management* and definitions for each are given in Table II below:

| Risk Management (RM) | The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk (ICH Q9 [4]) |
|----------------------|--------------------------------------------------------------------------------------------------|
| Quality Risk Management (QRM) | A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9 [4]) |
| Knowledge | Human or organizational asset enabling effective decisions and action in context (ISO 30401 [5])
  • Note 1: Knowledge can be individual, collective or organizational.
  • Note 2: There are diverse views on the scope covered within knowledge, based on context and purpose. The definition above is general as to the various perspectives. Examples of knowledge include insights and know-how.
  • Note 3: Knowledge is acquired through learning or experience |
| Knowledge Management (KM) | (1) Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components. (ICH Q10 [1])
(2) Management with regard to knowledge. (ISO 30401 [5])
  • Note 1: It uses a systemic and holistic approach to improve results and learning.
  • Note 2: It includes optimizing the identification, creation, analysis, representation, distribution and application of knowledge to create organizational value. |
2 Literature Review – Research on the Relationship of Risk Management & Knowledge Management

A review of the available literature was conducted to cast a broader lens beyond the biopharmaceutical industry on how risk management and knowledge management have been related by others.

2.1 Risk management and knowledge management

First, it is important to note that risk management and knowledge management share many of the same goals, in addition to the overarching goal of protection of the patient as a stated goal in biopharmaceutical regulatory guidance [6]. According to Lengyel et al. [7], these goals include supporting organizational action, sharing knowledge and enhancing risk-based decision making. Martin et al. [8] state a key goal of knowledge management 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, linking to knowledge management and risk management through the decision making process. A simple example of ensuring the right knowledge is available to reduce risk is provided by Kaplan and Garrick [9]. In this case, automobile drivers are provided the knowledge to make them aware about “a hole in the road around the corner,” in order to reduce the risk presented by the hole in the road to those drivers.

Webb [10] states risk management has a natural confluence with knowledge management. Sensing and responding to potentially damaging incidents is very much dependent on using organizational knowledge and intellectual capital to minimize risk, and that knowledge management can also be helpful in understanding how to best manage risk. Webb goes on to state that effective communication coupled with the development of a learning culture, with openness, lack of blame and a readiness to analyze and learn from past mistakes are all key tenets of a successful knowledge management program and are also key to effective risk management. Neef [11] asserts that “risk management is knowledge management” and states the key to a proactive risk management process lies in the company’s ability to mobilize the
knowledge and expertise of its employees so that organizational leaders can ensure they get accurate and timely information about a potentially harmful incident.

Nivolianitou [12] writes “all the aids of modern civilization such as advanced technology, chemical product and medicines have their dark sides, which are mainly investigated through the relatively new disciplines of risk analysis, risk assessment and risk management.” She goes on to discuss the classification of natural and industrial hazards and explains how difficulties in the management of those risks are “compounded by the fact that there is often great uncertainty associated with estimates of their nature”. She explains how such uncertainty is sometimes due to a “sparse database from which to derive risk estimates” and lacking knowledge “of the ways in which accidents, illnesses, or other forms of harm result from exposure to a technology”. On reflection, Nivolianitou is highlighting a key issue as technology advancement continues to accelerate and comprehensive knowledge and understanding lags behind.

Further to these examples, a comprehensive and useful review on understanding the relationship between risk management and knowledge management was conducted by Haltiwanger et al. [13] in 2010. Haltiwanger conducted an extensive literature review exploring how knowledge management is applied to managing risk (citing 12 papers), how risk management is applied to knowledge management (citing 6 papers), and the co-deployment of risk management and knowledge management (citing 6 papers). Haltiwanger asserts “risk management relies on the quality of knowledge and the efficient transfer of that knowledge”. Haltiwanger’s conclusion is consistent with the above citations in that there are convincing arguments for a substantial relationship between risk management and knowledge management, and that the principles of risk management are being applied to enhance knowledge management, while knowledge management is being used as a tool to improve risk management strategies. More research is required, however, to explore and define the various scenarios.
Concurrently published research by Massingham [14] into a proposed framework for “knowledge risk management (KRM)” reached a similar conclusion. Massingham identified two main themes very similar to Haltiwanger – how knowledge can reduce risk, leading to better risk management, and how the process of knowledge management can improve risk management. Massingham goes on to examine the effectiveness of conventional decision tree methods for organizational risk management and he presents an alternate model supported by knowledge management. He concludes that the inclusion of knowledge management offers managers deeper insight into the real nature of organizational risk. This is reinforced by Marshal, who states “risk management is frequently not a problem of a lack of information, but rather a lack of knowledge with which to interpret it’s meaning” [15].

After his detailed literature review in 2010, Haltiwanger [16] conducted additional research exploring the relationship between knowledge transfer and risk management. He asserts that knowledge transfer, specifically lessons learned, best practices and near misses, has a positive impact on risk management capabilities, as the more that is known about a task and the risks associated with that task, the higher the likelihood of success in completing that task. Haltiwanger then proposes a hypothesis that effective transfer of lessons learned, best practices and near misses (independent variables) positively impacted risk planning, risk identification, risk analysis, risk handling, risk monitoring and risk documentation (dependent variables). Through a survey and subsequent statistical analysis, the primary hypothesis was supported, that there is a causal relationship between the stated knowledge transfer aspects (lessons learned, best practices and near misses) and risk management capabilities. The paper acknowledged the relatively small sample size (90 survey responses) used and limitations in statistically predicting improvements in risk management through improved knowledge management.

Another area of focused study on this topic is in the area of aeronautics, particularly how NASA uses risk management and knowledge management in managing the risks presented by human spaceflight. NASA has a Risk Management Handbook [17] where extensive rigor has been put
into defining a risk management framework and a Risk-Informed Decision Making (RIDM) process. This handbook extensively links missing or incomplete knowledge with uncertainty and spells out specific expectations for knowledge management and risk management, including that risk management decisions and their rationales are captured as part of the institutional knowledge of the organization.

A PhD thesis was published by Lengyel in 2018 [18], which examines the relationships between risk management, knowledge management and decision making. Lengyel studied NASA’s Exploration Systems Mission Directorate (ESMD) experiment on Integrated Risk Knowledge Management (IRKM) framework. Among the many insightful conclusions reached by Lengyel is a list of how knowledge management improves risk management, as follows. This list is based on interview responses from NASA staff:

- Filled knowledge gaps in program/project/enterprise risks
- Developed a risk information sharing culture
- Improved individual and team communication modalities
- Enhanced and sped up process improvements
- Developed collaboration opportunities across the enterprise
- Enabled locating subject matter experts (through the risk database)
- Improved analytical problem solving and decision-making
- Captured and shared validated/best practices
- Ensured the capture and transfer of risk-based knowledge

Also explored in Lengyel’s thesis [18] were knowledge management–related challenges, which were reported as follows:

- Must overcome cultural resistance to sharing detailed risk data across a large portfolio of programs and projects
- Must overcome cultural resistance to do ‘lessons-learning’ in general
- Must set aside time for ‘lessons-learning’ in all programs and projects to avoid a heads-down, schedule and product-driven mentality
- Information technology tools and architecture should support cross-organization access to risk-based knowledge in a secure fashion to ensure effective knowledge sharing
• Risk Management Officers must be adequately resourced to perform risk and knowledge management duties

Another useful thought framework was shared by Browning [19]. Browning asserts that teams can only manage known risks and are largely unable to manage the “unknown-unknowns” – things we don’t know that we don’t know. Applying this thinking to the biopharmaceutical knowledge and risk management context, let’s consider the following construct:

• There are known-knowns. These are things we know that we know. This may be best described as prior knowledge, platform knowledge, all of the product and process knowledge accumulated on a given development program, and the like. A key outcome of knowledge management here is to ensure we are able to apply this knowledge during quality risk management activities, to ensure the best decisions and the lowest risk.

• There are known-unknowns. These are things we know that we don’t know. Examples of this would be unanswered questions we have during product development and a lack of knowledge about product performance beyond the boundaries of a design space. A key outcome of risk management here is to identify where new knowledge should be acquired to transform these questions into answers, and this new knowledge would feed into the knowledge management construct.

• There are unknown-unknowns. These are the things we don’t know that we don’t know. These are without doubt a primary source of risk (they are surprises!), and the goal here would be to minimize this category. While unknown-unknowns can never be eliminated, some are ‘knowable’ if techniques are applied to explore clues and take appropriate action.

Browning introduces the concept of directed recognition and presents a set of techniques and behavioral approaches – a combination of risk management and knowledge management – to minimize unknown-unknowns. The techniques include use of checklists, expert reviews of plans, long interviews, data mining, among others. The behavioral approaches include effective and frequent communication, a balance of local autonomy and central control, incentivizing discovery, and cultivating an alert culture.

2.2 Summary of Findings

As this literature review demonstrates, the interplay between managing risk and managing knowledge is not new. For the last 20+ years this has been a topic of discussion as presented
above, spanning finance, legal, information technology, aerospace, corporate risk management, military and other domains. The findings are consistent, that there is a direct relationship between knowledge and risk – the more knowledge (leading to increased understanding and decreased uncertainty), the lower the risk. And increased knowledge and decreased risk lead to improved decision making and better decision outcomes.

3 Literature Review – Regulatory Guidance Linking Risk Management and Knowledge Management

A review of regulatory guidance documents was conducted to examine the relationship between risk and knowledge and their respective disciplines of risk management and knowledge management. This review was conducted as a means to better understand the relationship and characterize it.

The following regulatory documents were examined:

- ICH Q8(R2): Pharmaceutical Development [20]
- ICH Q9: Quality Risk Management [4]
- ICH Q10: Pharmaceutical Quality System [1]
- ICH Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) [21]
- ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management [22]
- WHO Guidelines on Quality Risk Management [23]
- EudraLex Volume 4 – Good Manufacturing Practice (GMP) Guidelines (Parts I, II and IV) [6], [24], [25]
- PIC/S Guide to Good Manufacturing Practice for Medical Products (Part 1, Chapter 1) [26]
- ISO 14971: Medical Devices – Application of Risk Management to Medical Devices (Third Edition 2019-12) [27]
- FDA Guidance for Industry – Process Validation: General Principles and Practices [28]
3.1 ICH Q8(R2): Pharmaceutical Development
ICH Q8 [20] links knowledge management and quality risk management citing knowledge as both an input:

*Risk assessment tools can be used to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data*

and as an output to the quality risk management process:

...*knowledge gained during application of scientific approaches and QRM;*

*Appropriate use of quality risk management principles can be helpful in prioritising the additional pharmaceutical development studies to collect such knowledge*

ICH Q8 establishes an initial basis for a symbiotic relationship between quality risk management and knowledge management.

3.2 ICH Q9: Quality Risk Management
ICH Q9 [4] is specifically dedicated to quality risk management as a “systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the lifecycle.” Of note, quality risk management is a ‘twin enabler’ to knowledge management [1] yet there is no corresponding guidance established for knowledge management as a parallel to ICH Q9 for quality risk management.

Early on, ICH Q9 identifies two primary principles of quality risk management, the first of which is:

*The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient*

Said differently, (scientific) knowledge drives the quality risk management process. ICH Q9 also states that a source of uncertainty (about risk) is driven by gaps in knowledge (i.e. missing knowledge will hinder effectiveness of the risk assessment).
While ICH Q9 does not refer to knowledge management directly, it clearly establishes knowledge as a key input to effective quality risk management, affecting the assessment of the probability, severity and sometimes detectability of a risk.

3.3 ICH Q10: Pharmaceutical Quality System

ICH Q10 [1] presents the concept of knowledge management as part an organization’s pharmaceutical quality system and goes on to establish knowledge management along with quality risk management as enablers to an effective pharmaceutical quality system. Figure 1 is the well-recognized image from ICH Q10 which depicts these enablers relative to the rest of the pharmaceutical quality system.

![Figure 1 - The pharmaceutical quality system per ICH Q10](image-url)
ICH Q10 perhaps most succinctly links knowledge management and quality risk management as a means to ensure informed, sound decisions, in particular related to product quality as follows:

“Use of knowledge management and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives (of ICH Q10) by providing the means for science and risk-based decisions related to product quality.”

Knowledge management and quality risk management are repeatedly cited as central to the goals of the PQS and as inputs to key processes described within ICH Q10, including the control strategy and change management.

A more subtle relationship between knowledge management and quality risk management is also evident in ICH Q10. ICH Q10 relates knowledge and risk directly, as cited throughout this section. ICH Q10 also links that knowledge is the basis for understanding, for example from Section 1.6.1 on Knowledge Management:

Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding.

This linkage is repeated elsewhere in ICH Q10. Therefore, while knowledge and understanding are not equivalent as implicitly defined in ICH Q10, understanding also has a link to risk and this is dependent on knowledge. For example, in Annex 1 multiple scenarios are presented as opportunities to enhance science and risk-based regulatory approaches. These include scenarios to:

- Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).

- Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).
In these examples, understanding is not possible without knowledge, and therefore these are additional examples, albeit less obvious, where knowledge management and quality risk management are connected.

3.4 ICH Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)

ICH Q11 [21] immediately links risk management and knowledge in its introduction as a means to deliver on control strategies and definition of the design space:

_In an enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that impact critical quality attributes (CQAs) and develop appropriate control strategies applicable over the lifecycle of the drug substance which may include the establishment of design space(s)._ 

In the Process Development Tools section, quality risk management and knowledge management are cited as the two process development tools as a general principle for the guideline and referenced repeatedly as means to justify important aspects of the manufacturing process.

3.5 ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

ICH Q12 [22] links knowledge and risk in the introduction, stating:

_{This guideline is also intended to demonstrate how increased product and process knowledge can contribute to a more precise and accurate understanding of which post-approval changes require a regulatory submission as well as the definition of the level of reporting categories for such changes (i.e., a better understanding of risk to product quality).}_

Or said differently, knowledge is the basis of understanding risk. ICH Q12 continues to relate the level of knowledge to the effectiveness of a risk assessment of changes and associated product and process understanding.
3.6 WHO Guidelines on Quality Risk Management – Annex 2

The World Health Organization (WHO) guideline on Quality Risk Management [23] has perhaps the most explicit connections between knowledge and knowledge management with quality risk management. Relevant examples include:

QRM should ensure that...the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient

The QRM approach may be used to...facilitate the transfer of process knowledge and product development history to ease product progression throughout its life-cycle and to supplement already available knowledge about the product;

Early in development, the purpose of the QRM process may be to acquire sufficient product and process knowledge to assess risks associated with formulation development of the finished pharmaceutical product (FPP) according to the quality target product profile (QTPP). In recognizing risks and knowledge gaps, the QRM process plays a significant role in proactively enabling the prioritization and mitigation of risks. The objective is to develop the FPP through maximizing product and process knowledge and risk mitigation.

A crucial aspect of product development and QRM is the maintenance of an effective and secure knowledge management and documentation system. Such a system must facilitate transparent communication and the highlighting of key issues to stakeholders and must also include a well-structured archive. Clearly, the ability to organize diverse data and information effectively and then retrieve it as required for updating and further evaluation, e.g. for the purposes of process validation, would be hugely beneficial.

Personnel involved in QRM: The implementing party, i.e. the pharmaceutical manufacturer or regulatory authority, should assure that personnel with appropriate product-specific knowledge and expertise are available to ensure effective planning and completion of QRM activities.

Knowledge of the product and process - QRM should be based on knowledge of the product or processes concerned, according to the stage of the product life-cycle.

As product knowledge advances, more detailed QRM exercises can be considered
Inspection of QRM at a manufacturing site Note: During inspections, inspectors should assess whether a manufacturer has appropriate skills and scientific knowledge, as well as product and process knowledge, for the QRM procedure being inspected.

Clearly management of knowledge and QRM are tightly intertwined in the eyes of the WHO.

3.7 EudraLex Volume 4 – Good Manufacturing Practice (GMP) Guidelines (Part I - Chapter 1 and Part II – Section 2.2)

Chapter 1 of the EU GMP Guide, titled ‘Pharmaceutical Quality System’ [6], explicitly positions knowledge (both explicit and tacit) as an input to quality risk management; this highlights the links between quality risk management and knowledge management, as follows:

The principles of quality risk management are that... The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient.

Note that this is essentially the first QRM principle from ICH Q9 re-stated, but with a reference to process experience added in.

Similarly, in Part II of the EudraLex Vol. 4 Guidelines, which addresses the GMP expectations for active substances used as starting materials, there is a slightly modified version of the above principle, as follows:

The quality risk management system should ensure that: - the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient through communication with the user of the active substance.

3.8 EudraLex Volume 4 – Good Manufacturing Practice (GMP) Guidelines (Part IV - Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products)

The EudraLex Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (ATMP) [25] in Section 2.2 on Application of the risk-based approach by
ATMP manufacturers links knowledge as an input to both risk evaluation and risk control and mitigation:

*The evaluation of the risks and the effectiveness of the control/mitigation measures should be based on current scientific knowledge and the accumulated experience. Ultimately, this evaluation is linked to the protection of patients.*

3.9 **PIC/S Guide to Good Manufacturing Practice for Medicinal Products (Part 1, Chapter 1)**

This is essentially the same as Chapter 1 of the EU GMP Guide which is [26] referred to above, and it has the same principle of QRM stated in it as above, which links quality risk management and knowledge management.

3.10 **ISO 14971: Medical Devices – Application of Risk Management to Medical Devices (Third Edition 2019-12)**

The ISO international standard 14971 on Application of Risk Management to Medical Devices [27] identifies knowledge as an input to multiple phases of risk management. In particular this guideline emphasizes the tacit and other experiential knowledge in people (described as *competence of personnel*) as follows:

*It is most important to get competent people with the knowledge and experience necessary to perform risk management tasks. The risk management process requires people with knowledge and experience in areas such as:*

- How the medical device is constructed;
- How the medical device works
- How the medical device is produced;
- How the medical device is actually used;
- How to apply the risk management process.

3.11 **FDA Guidance for Industry – Process Validation: General Principles and Practices**

The FDA guidance document issued in 2011 Process Validation: General Principles and Practices [28] in the section on *Building and Capturing Process Knowledge and Understanding* identifies
risk management as a means to identify knowledge gaps and thus knowledge (and the need for knowledge creation – i.e. ‘known-unknowns’) is an output to risk management:

*Risk analysis tools can be used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained.*

### 3.12 Summary of Regulatory Guidance Literature Review

Collectively the themes of knowledge and risk, along with knowledge management and risk management as structured means to manage each, are prevalent and persistent across the diverse set regulatory literature reviewed. The intent of this review is also to look beyond an explicit and obvious description stating how risk management and knowledge management are linked, as if this existed, this review would not be necessary. The intent is to examine the more subtle instances of how knowledge and risk are connected, in addition to knowledge management and risk management, even though these latter terms are used less frequently (especially knowledge management). Further, this review also extends to the FDA vision of science and risk-based quality for the 21st century [2], given the inseparability of knowledge and science.

Many of these links are evident although some are less obvious as the words ‘knowledge’ and ‘risk’ are not used directly adjacent, such as where ICH Q10 [1] extends knowledge to increased understanding as discussed above. This review was conducted in an attempt to illustrate the presence of these linkages, there are certainly more direct and indirect linkages which exist.

As the citations demonstrate, knowledge and risk bear a clear relationship, with knowledge being recognized as both an input and an output to quality risk management. This leads to greater control of risks to quality through increased understanding. In addition, this risk control may involve addressing knowledge gaps (“known-unknowns”), which in turn leads to increasing knowledge. The two are each interwoven: knowledge & risk, and knowledge management & risk management.
According to the WHO guideline on Quality Risk Management [23], an “effective and secure knowledge management system” is crucial to quality risk management. This guideline also highlights the expectations for using not only documented knowledge (explicit knowledge), but also establishes the expectation for using the knowledge “in the heads of people” where experience and expertise are critical (tacit knowledge). Figure 2, drawn by the author, provides a simple depiction relating knowledge, knowledge management, risk and risk management. An important caveat is that it is impossible for knowledge management to manage all knowledge as it is for quality risk management to manage all risk, and this is not meant to be inferred in Figure 2. Yet these respective disciplines are crucial to provide a thoughtful, standardized and programmatic structure to each of the domains of knowledge and risk.

![Figure 2 - Relating knowledge, knowledge management, risk and risk management](image)

It is the hope of the authors that this aggregated view across many guidance documents has clearly illustrated this interdependency and in turn, created the case for more synergy between quality risk management and knowledge management.
4 Discussion of Literature Review Findings

This is perhaps a timely analysis given the ongoing efforts by the industry on quality risk management and knowledge management, and the increasing recognition of the relationship between the two. For example, at the 2020 PDA Europe Quality & Regulations Conference (held virtually on 09-11 June 2020), several presenters, including members of the PRST touched on the connection.

David Churchward, MHRA, in his presentation titled Control Strategies: A Foundation for Quality and Regulatory Flexibility [29] explained that control strategies enhance effectiveness of individual control measures by taking a holistic approach in linking to product and process knowledge, quality risk management and the pharmaceutical quality system. This changes the focus from considering each control separately to designing coordinated and proactive measures that deliver quality outcomes greater than the sum of those activities.

Kevin O’Donnell, HPRA one of the authors of this paper in a presentation titled A Regulator’s Perspective on Quality Risk Management & Knowledge Management after 12 Years [30] reflected on the journey of each practice. O’Donnell suggests assessing the effectiveness of knowledge management activities based on their risk reduction benefit, and asserts:

• As knowledge increases, uncertainty should decrease, and risk should decrease

• An effective use of knowledge in quality risk management activities should drive risk down

• ISO 31000 on Risk Management defines risk as “the effect on uncertainty on objectives”, where uncertainty relates to a deficiency in one’s knowledge of an event, its consequence or likelihood.

Further, the literature review above supports O’Donnell’s suggestion made during the same presentation that QRM has been of ‘foundational relevance’ and major GMP revisions and guidelines have included a heavy emphasis on QRM. However, O’Donnell also notes the KM
story “is a lot shorter,” recognizing a deficiency of knowledge management references in GMP revisions and guidelines.

Another author of this paper, Martin Lipa (PRST), in a recent paper exploring the effectiveness of knowledge transfer during technology transfer [31] cited several examples linking knowledge management and risk from expert interviews of industry leaders and regulatory authorities, including residual latent risk, for which improved knowledge management could deliver benefit.

Emma Ramnarine (PRST) in a lecture at TU Dublin entitled “Quality Risk Management Application for Technology Transfers in November 2019 depicted that product and process knowledge (as well as knowledge about the patient requirements and design specifications) are inputs to quality risk management which then produces outputs including identification of critical quality attributes and critical process parameters (Figure 3). Ramnarine further asserted a quote by Irving Fisher [32] that “risk varies inversely with knowledge.”
This quote nicely sums up many of the previous citations. However, in the opinions of the authors of this paper, this over-simplifies a key point in that it is really the application of knowledge that is required to reduce risk. The knowledge must have been created, identified, stored, accessible – and it must flow to when and where it is needed to inform the risk evaluation (i.e. the right knowledge to the right person at the right time). This is the fundamental discipline of knowledge management – it is the collection of practices which enable both explicit knowledge and tacit knowledge to flow to drive business outcomes – which in this context is risk management. While especially true in large complex organizations, there are many other barriers to knowledge flow, including the passing of time, changes in personnel,
functional boundaries ("silos"), differences in work processes, organizational hierarchy, and suppler and customer relationships – just to name a few.

Figure 4 developed by Lipa illustrates this concept. In the figure risk is depicted as function of knowledge application. The more knowledge available – and applied – the greater the understanding (and the lower the uncertainty) – and therefore the lower the risk. In an ideal world, the minimum risk would approach zero ($\text{Risk}_{\text{min}}$) (green line) when sufficient knowledge is acquired about a given topic, whether through robust prior knowledge, during product development, or as a result of experience over time. One could envision a complete mechanistic understanding of a topic and rich experience built in to prevent and control risk would result in an attractive and relatively low risk profile.

**Risk varies inversely with Knowledge Applied**

*Goal: To minimize risk to the patient by applying the most complete and accurate body of knowledge*

$$\text{Risk} = f (\text{knowledge}_{\text{applied}})$$

*Meaning: Risk is a function of knowledge application...the more knowledge, the less risk*

$$\text{Knowledge}_{\text{applied}} = f (K \text{ flow, K availability, K capture, K accuracy, ...})$$

*Meaning: for knowledge to be applied, it must be available, it must flow to when and where it is needed, it must have been captured, it must be accurate, ...; all direct goals of a KM program*

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*Figure 4 - Risk varies inversely with knowledge applied*
In reality, the actual risk (Risk_{actual}) is higher (as depicted by the purple line in Figure 4) as there is an inherent lack of knowledge if quality risk management is not fully enabled by knowledge management. The literature review in Section 2 repeatedly highlights this point, which is perhaps most tangibly identified by the research of Lengyel [18] who discusses the quality risk management benefits associated with improved knowledge management.

A lower level of risk is achievable (Risk_{achievable}) (as depicted by the blue line in Figure 4) if knowledge application is maximized. This presents the opportunity for knowledge management to reduce risk and improve quality risk management outcomes. As depicted, there are a number of dependencies for knowledge to be applied to risk management (or in any other context) – including the knowledge flowing to when and where it is needed, it is available and accessible, it has been captured to being with, it is accurate – and others. These are all key goals of a thoughtful knowledge management program of which quality risk management can be a knowledge consumer. As stated by Verhaegen [33], “knowledge makes risks manageable.”

5 Conclusion

Given the concept that risk varies inversely with knowledge applied, for the biopharmaceutical industry one might ask: Do current quality risk management programs:

- Leverage expertise locators to ensure the best possible expertise and experience is leveraged for a quality risk management exercise, not just the ‘usual suspects’? Leverage diversity of thought within the organization that may exist at different levels and across different products, modalities, etc.?

- Leverage a rich database of quality lessons learned?

- Leverage the connectivity and tacit knowledge of communities, to help recognize, communicate and mitigate risk?

- Leverage a robust source of product, process and standardized platform knowledge?

- Is risk continually reduced by leveraging best practices and proven mitigation actions?
• Benefit from a culture that manages knowledge as an asset, as well as a knowledge seeking and sharing culture?

• Use knowledge management practices to reduce unknown-unknowns?

• Are knowledge management principles fully embedded in quality risk management to ensure the knowledge created during quality risk management (e.g. decision rationale) are sufficiently captured and available for the future?

The authors believe, that the impact of quality risk management and knowledge management when leveraged together can be greater than the sum of the parts. This starts with the organization viewing knowledge as an asset [34], [35] and leveraging all available knowledge assets routinely in the practice of risk management. Quality risk management should be a source of demand and driving knowledge management practice requirements, both for knowledge inputs and outputs of the quality risk management process. And knowledge management should be ready to meet these requirements and accelerate risk reduction by ensuring the right knowledge is available to the right person at the right time. One can’t perform a risk assessment and just expect the best possible knowledge to magically appear without some thought for how that knowledge has been captured and curated to be available on demand. As asserted by Lelic [36] “an organization can’t manage its risk today without managing its knowledge.” ICH Q10 has famously paired these powerful processes and rightly recognized them as enablers to quality through their ability to facilitate higher quality products.

Yet each discipline appears to have largely embarked on their own journey in pursuit of excellence.

Consider the following list of recurring issues blamed for accidents at NASA across 8 programs: [37]

• Lack of rigor in engineering processes
• Inadequate technical and peer review process
• Poor documentation and communication of changes
• Incomplete risk management/analysis
• Lack of appropriate simulation, verification, and test, including “test as you fly”
• Inappropriate application of heritage design/hardware
• Mission operations issues
• Inadequate training and experience
• Schedule pressure
• Ineffective communication of NASA’s lessons learned

There is certainly a similar story – perhaps not as clear or dramatic as a failure in space – playing out in the biopharmaceutical industry, affecting quality, cost, development timelines and availability of biopharmaceutical products to patients. It does not take much ingenuity to recognize that quality risk management and knowledge management can each have a positive impact on many of the items on the list of recurring issues discovered by Curtis.

And while there is the opportunity for continual improvement in each of the individual disciplines of quality risk management and knowledge management, the need to more seamlessly integrate is important, in the opinion of the authors, while still allowing them to remain as independent practices. They each have their respective place in the business and fully integrating them into one entity risks generalization which could for example, dilute some of the other drivers of knowledge management, including business efficiency, process improvement and employee engagement.

Additional study is well warranted in the relationship of knowledge management and quality risk management for the biopharmaceutical sector. A variety of topics surfaced during the course of research in preparing this paper. One area of interest is to explore how quality risk management and knowledge management might interact with each other during the course of risk management activities. Another potential area of focus is expert opinion elucidation which is more than surfacing tacit knowledge and is influenced by certain heuristics. This has not been well studied in the context of the biopharmaceutical sector, which could benefit in how expert knowledge is applied to risk management in a more objective fashion. A third potential area of attention could support exploring a continuum from risk-based decision making through to knowledge-based decision making.
Perhaps the response of the biopharmaceutical industry in collaborating in a whole new way in response to COVID-19 will reveal some hints as to the power of knowledge flowing in a much more frictionless way.

**Disclaimer**
The views expressed in this article are those of the authors and are not necessarily those of the Health Products Regulatory Agency (HPRA) or Merck & Co., Inc. (Kenilworth, NJ USA).

**Bibliography**

[1] International Conference on Harmonisation, *Quality Guideline Q10: Pharmaceutical Quality System*. Geneva, 2008.

[2] US FDA, “Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach (FDA Press Release, No. P02-28),” *FDA News*, Aug. 21, 2002.

[3] A. Greene and K. O’Donnell, “From Science to Knowledge: An Overview of the Evolution of Knowledge Management in Regulatory Guidance,” *Pharmaceutical Engineering: e-supplement on Knowledge Management*, no. May 2014, pp. 44–48, 2014, [Online]. Available: http://www.ispe.org/pharmaceutical_engineering/knowledge-management-supplement.

[4] International Conference on Harmonisation, *Quality Guideline Q9: Quality Risk Management*. Geneva, 2005.

[5] ISO, “ISO 30401 - Knowledge management systems - Requirements,” Geneva, 2018. [Online]. Available: https://www.iso.org/standard/68683.html.

[6] European Commission, “EudraLex Volume 4 - Part 1: EU Guidelines for GMP for Medical Products for Human and Veterinary Use; Chapter 1 - Pharmaceutical Quality System,” *European Commission Health and Consumers Directorate-General*, vol. 4, no. January 2013, p. 8, 2012.

[7] D. Lengyel, “Integrating risk and knowledge management in human space flight programs,” *Online Journal of Applied Knowledge Management*, vol. 7, no. 2, 2019, doi: 10.36965/ojakm.2019.7(2)1-15.

[8] I. Martin, A. Prior, V. Ward, C. Holtham, and A. Prior, “People and patterns: a case study of the relationship between risk management and knowledge management in financial services,” vol. 44, no. 0, pp. 1–17, 2002.

[9] S. Kaplan and B. J. Garrick, “On the Quantitative Definition of Risk,” *Risk Analysis*, vol. 1, no. 1, pp. 11–27, 1981.

[10] J. Webb, “Risk Management Report and Tool Kit,” *FreePint*, vol. 222, 2007.

[11] D. Neef, “Managing corporate risk through better knowledge management,” *The Learning Organization*, vol. 12, no. 2, pp. 112–124, 2005, doi: 10.1108/09696470510583502.

[12] Z. Nivolianitou, “Risk analysis and risk management: a European insight,” *Law, Probability and Risk*, vol. 1, no. 2, pp. 161–174, 2002, doi: 10.1093/lpr/1.2.161.
[13] G. Haltiwanger, R. E. Landaeta, C. A. Pinto, and A. Tolk, “Understanding the relationship between Risk Management and Knowledge Management: A literature review and extension,” *International Journal of Knowledge Management Studies*, vol. 4, no. 3, pp. 281–300, 2010, doi: 10.1504/IJKMS.2010.038170.

[14] P. Massingham, “Knowledge risk management: A framework,” *Journal of Knowledge Management*, vol. 14, no. 3, pp. 464–485, 2010, doi: 10.1108/13673271011050166.

[15] C. Marshall, L. Prusak, and D. Shpilberg, “Financial risk and the need for superior knowledge management,” *California Management Review*, vol. 38, no. 3, 1996, doi: 10.1016/b978-0-7506-9718-7.50014-7.

[16] G. S. Haltiwanger and J. A. Temple, “Establishing relationships between risk management and knowledge transfer,” 2014 *International Annual Conference of the American Society for Engineering Management - Entrepreneurship Engineering: Harnessing Innovation, ASEM 2014*, 2014.

[17] National Aeronautics and Space Administration, “NASA Risk Management Handbook NASA/SP-2011-3422,” no. November 2011, p. 256, 2011, [Online]. Available: https://ntrs.nasa.gov/search.jsp?R=20120000033 2020-03-18T02:54:48+00:00Z.

[18] D. Lengyel, “A Critical Examination of the Relationships Between Risk Management, Knowledge Management and Decision Making,” 2018.

[19] T. R. Browning and R. v. Ramasesh, “Reducing unwelcome surprises in project management,” *MIT Sloan Management Review*, vol. 56, no. 3, pp. 53–62, 2015.

[20] ICH, “Pharmaceutical Development Q8 (R2),” *ICH Harmonised Tripartite Guideline*, vol. 8, no. August, pp. 1–28, 2009.

[21] ICH, “International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Implementation Working Group ICH Q11 Guideline: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities),” 2017.

[22] International Conference on Harmonisation, *Quality Guideline Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*. Geneva, 2019.

[23] WHO Expert Committee on Specifications for Pharmaceutical Preparations, “Annex 2 WHO guidelines on quality risk management,” *Forty seventh report*, pp. 61–92, 2013.

[24] European Commission, *EudraLex Volume 4 - Part II: Basic Requirements for Active Substances used as Starting Materials Status*. Belgium, 2014.

[25] European Commission, *EudraLex Volume 4 - Part IV - Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products*, no. November. Belgium, 2017.

[26] PIC/S Secretariat, *Guide to Good Manufacturing Practice for Medicinal Products - Part 1*, no. July. Geneva, 2018.

[27] International Organization for Standardization, “ISO 14971_2019 - Medical Devices - Application of Risk Management,” Geneva, 2019.

[28] US FDA, “Guidance for Industry - Process Validation: General Principles and Practices,” 2011.

[29] D. Churchward, “Control Strategies : A foundation for quality and regulatory flexibility,” 2020.

[30] K. O. Donnell, “A Regulator’s Perspective on Quality Risk Management & Knowledge Management after 12 Years QRM & KM – the Twin Enablers in ICH Q10,” 2020.
[31] M. Lipa, P. E. Kane, and A. Greene, “Effective Knowledge Transfer During Biopharmaceutical Technology Transfer - How Well Do We Do It?,” *IVT Network*, vol. 25, no. 4, 2019, [Online]. Available: https://www.ivtnetwork.com/article/effective-knowledge-transfer-during-biopharmaceutical-technology-transfer-0.

[32] I. Fisher, *The Rate of Interest: Its Nature, Determination and Relation to Economic Phenomena*. New York: Macmillan, 1907.

[33] T. Verhaegen, “Knowledge makes risks manageable,” *Business Insurance*, pp. 1–3, 2005, [Online]. Available: https://search.ebscohost.com/login.aspx?direct=true&db=edsgbe&AN=edsgcl.130863770&site=eds-live.

[34] M. Lipa, S. Bruno, M. Thien, and R. Guenard, “A Practical Approach to Managing Knowledge- A Case Study of the Evolution of KM at Merck,” *ISPE Knowledge Management e-Journal*, vol. 33, no. 6, pp. 8–18, 2014.

[35] P. Kane, “A Blueprint for Knowledge Management in the Biopharmaceutical Sector,” 2018.

[36] S. Lelic, “Managing Knowledge to Manage Risk,” *Knowledge Management*, vol. 6, no. 1, 2002.

[37] L. Curtis, “NASA Mishap Investigation Review: Application To LRO And LCROSS,” 2007.