Exploring the Risk-Knowledge Infinity Cycle (RKI Cycle) across the Product Lifecycle

Case studies demonstrating the link between knowledge and risk in technology transfer and commercial manufacture.

Authors:
Martin J. Lipa, TU Dublin Pharmaceutical Regulatory Science Team (PRST) | martin.lipa@prst.ie
Valerie Mulholland, TU Dublin Pharmaceutical Regulatory Science Team (PRST) | valerie@gmp.ie
Kevin O'Donnell, Health Products Regulatory Authority (HPRA) | kevin.odonnell@hpra.ie
Anne Greene, Technological University Dublin & TU Dublin PRST | anne.greene@TUDublin.ie

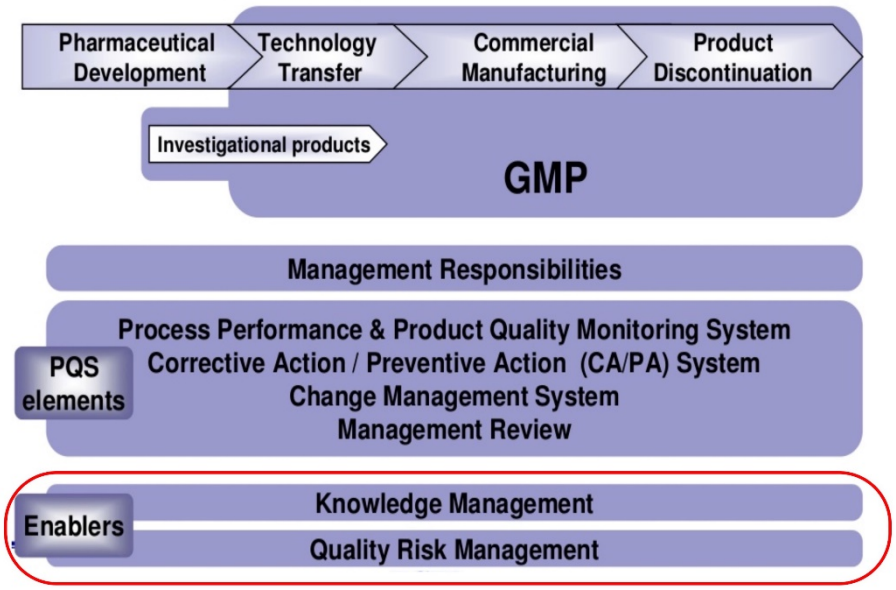
Preface

Quality Risk Management (QRM) and Knowledge Management (KM) are positioned as dual enablers to an effective Pharmaceutical Quality System. While there is broad agreement QRM and KM are highly interdependent in principle, there is recognition they are not well integrated in practice, and better integration is an opportunity to better manage risk and thus, increase patient protection. A framework, the *Risk-Knowledge Infinity Cycle (RKI Cycle)*, has been proposed to better integrate QRM and KM which can be applied across the entire product lifecycle. Details of the framework are explored and application of the *RKI Cycle* to the Commercial Manufacturing and Technology Transfer lifecycle phases is illustrated through multiple short case studies, including examples to demonstrate the benefits of effective tacit knowledge transfer. A re-imagined PQS foundation is presented, enabled by QRM and KM as intentionally connected and synergistic practices, as a means to reduce risk and ultimately benefit patients.

1 Introduction

ICH Q10, *Pharmaceutical Quality System* [1] provides a well-known depiction of an effective Pharmaceutical Quality System (PQS) (Figure 1.1), where Quality Risk Management (QRM) and Knowledge Management (KM) are positioned as dual enablers. These enablers are foundational to all four elements of the PQS and across the entire product lifecycle, from pharmaceutical development through to product discontinuation and are depicted in the ICH Q10 diagram as two independent horizontal bars.

Figure 1.1: KM and QRM as Dual Enablers of a Pharmaceutical Quality System [1]



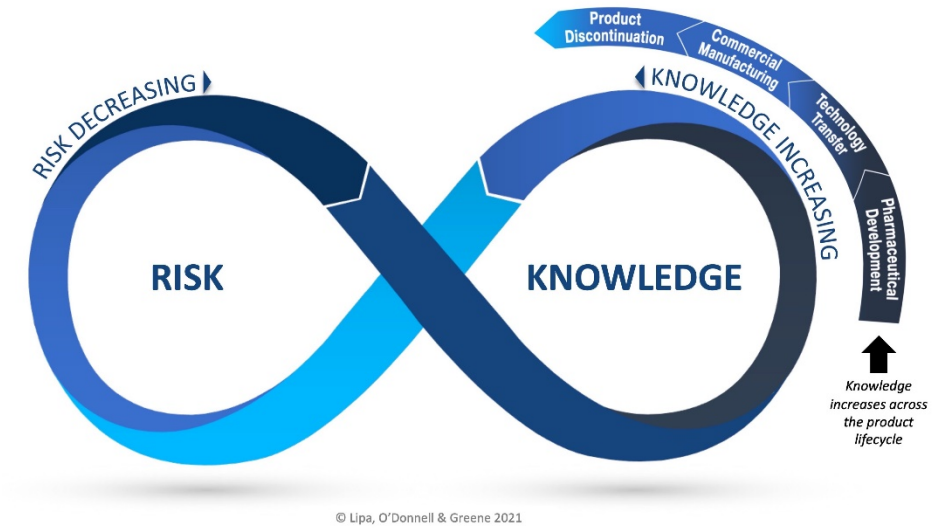
It is well established in ICH Q9, *Quality Risk Management* [2], that the purpose of QRM is to manage risk across the product lifecycle by applying the best scientific knowledge available to the organization *in order to* reduce risk to the patient. However, the purpose of KM is less widely understood. The authors propose that the purpose of KM in the context of the PQS is to deliver the best available knowledge to the right person at the right time *in order to* make the best possible decisions. In the context of the PQS, these decisions include evidence-based decisions made as part of an overall quality risk management process.

Furthermore, is has been established that risk varies inversely with knowledge [3]. Increased knowledge provides improved understanding. Improved understanding in turn leads to decreased uncertainty – and when applied appropriately – to lower risk. The idea that knowledge must be actively *applied* to realize this risk reduction recognizes that risk reduction does not happen by chance. It is this ability of the company to effectively apply the best of what it knows – to minimize risk - that is important, as effectively managing knowledge is critically important when aiming for a fully effective QRM program.

2 Integrating Knowledge and Risk across the Product Lifecycle

The interrelationship between the dual PQS enablers of QRM and KM has been explored by Lipa et al. [4], who suggested that the two disciplines should be more intentionally linked, and in turn developed the *Risk-Knowledge Infinity Cycle* (henceforth referred to as the *RKI Cycle*) as a means to foster improved integration, depicted in Figure 2.1.

Figure 2.1: The Risk-Knowledge Infinity Cycle (RKI Cycle) Applies across the Pharmaceutical Product Lifecycle



Key concepts supporting the *RKI Cycle* include [4]:

- Knowledge is both an input and output to risk management
- Knowledge has an inverse relationship with risk
- In an ideal state, knowledge flows effortlessly and on demand to inform risk, and risk informs new knowledge
- The cycle is continuous and perpetual; knowledge is always evolving and should be continually applied to inform risk, hence the symbolic nature of the infinity cycle
- Early in the product lifecycle when less is known about a product, risk is higher; over time knowledge increases through application of prior knowledge, development activities, manufacturing experience, risk review, investigations, innovations (etc.), and it can be applied to reduce risk
- The Risk/Knowledge relationship can be applied to any type of risk management activity, not just QRM

As the product progresses through the pharmaceutical product lifecycle, described in ICH Q10 as *Pharmaceutical Development*, *Technology Transfer*, *Commercial Manufacturing* and *Product Discontinuation*, the opportunity to gain and apply new knowledge occurs continually during each lifecycle stage, as depicted in Figure 2.1. Arguably, this is core to the very intent of ICH Q10: that product and process knowledge is managed across the lifecycle ***so that*** timely, informed, and effective risk-based decision-making can occur, ***so that*** the goals of ICH Q10 can be achieved (i.e., product realization, a state of control, and a basis for continual improvement).

A high-level review of each lifecycle stage, areas of emphasis where knowledge is required, and associated opportunities to apply KM was performed by Lipa and Kane [5] in 2021, and a comprehensive mapping of KM methods and tools across the pharmaceutical product lifecycle was carried out, as summarized in Table 2.1.

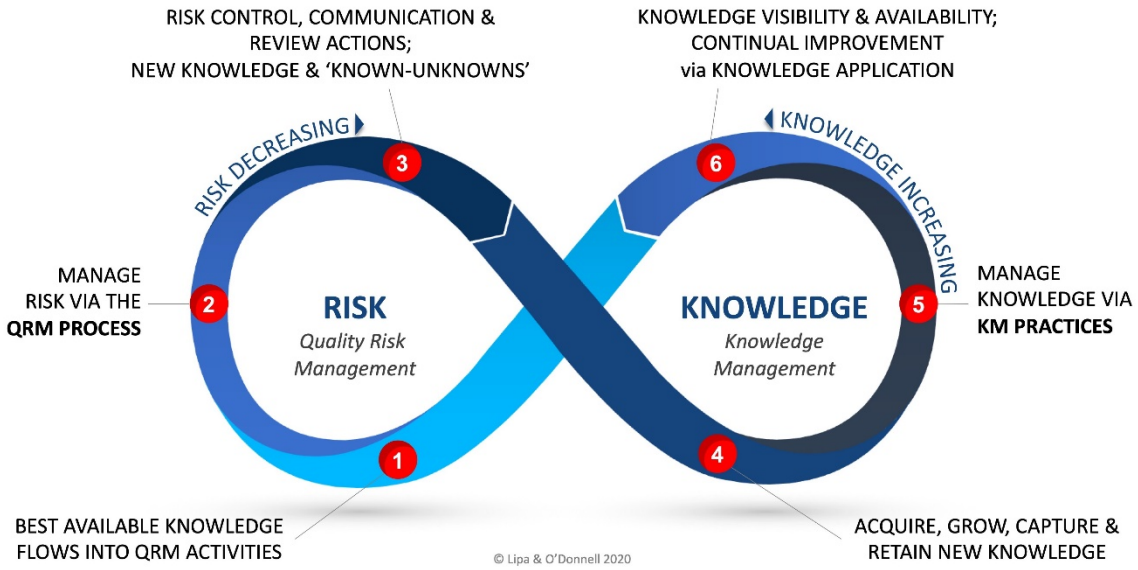
Table 2.1: Mapping of KM Opportunities across the Product Lifecycle [5]

Lifecycle Stage	Areas of Emphasis Where Knowledge is Required	How Knowledge Management can Provide Benefit (via Both Explicit and Tacit Knowledge)
Pharmaceutical Development (Product Development)	▪ Application of prior knowledge for risk assessments to determine areas of study ▪ Development work to capture new knowledge ▪ Ongoing risk assessment and risk control	▪ KM facilitates access to prior knowledge (platform technologies, other products, expertise in the company via individuals and Centers of Excellence (CoEs), external scientific literature, prior learnings and lessons, etc.) ▪ KM helps capture new knowledge during early development work (both what worked and what didn't) ▪ KM helps organize the records of product development and scientific knowledge, design choices, and other decision rationale
New Product Introduction / *Technology Transfer*	▪ Application of knowledge for risk assessments ▪ Comprehensive knowledge transfer ▪ Opportunity to learn more about the product/process ▪ Supporting the goal to ensure a right-first time transfer, robust process, and capable receiving site	▪ KM facilitates access to comprehensive product and process knowledge, including development and manufacturing history, including key decisions, learnings from failures, changes, etc. ▪ KM provides access to subject matter experts / personnel with process experience ▪ KM helps capture new product and process learnings and lessons learned
Commercial Manufacturing / Continual Improvement	▪ Ongoing knowledge build through accumulated manufacturing experience ▪ Lifecycle management, including planned and unplanned changes ▪ Seek to minimize disruptions to product availability by rapid problem solving and solving problems at root cause	▪ KM helps capture learnings, knowledge, and understanding of the product/process. ▪ KM provides knowledge visibility and availability across the full product lifecycle (including development) to support process monitoring, continual improvement, change management, investigations, etc. ▪ KM supports problem solving and sharing of best practices and improvements across the supply chain and back to the development organization.
Product Discontinuation	▪ Knowledge transfer for archival and future access on demand ▪ Harvesting learnings to inform “prior knowledge”	▪ KM helps capture knowledge in a complete and structured manner to allow for its future use (e.g., knowledge about stability, complaints, etc.) ▪ KM helps capture learnings including insights about platform technologies and other potential “prior knowledge.”

Note: These are illustrative concepts and not an exhaustive listing.

A recent survey reported that although QRM and KM are considered highly interdependent as theoretical concepts, the practical integration of QRM and KM has lagged [6]. The survey results also suggest that implementing a framework such as the *RKI Cycle* to better unite QRM and KM has the potential to enable a variety of significant benefits including better risk-based decisions, improved control strategies, and more.

Figure 2.2: The RKI Cycle as Applied to ICH Q10 [4]



Exploring the *RKI Cycle* in more detail reveals a cyclical, continuous process that shows the potential connection between QRM and KM. Starting with Node 1, the best available knowledge flows into QRM activities (i.e., these are knowledge *inputs* to QRM), facilitating risk assessments that occur at Node 2. Node 3 is where risk control, risk communication, and risk review activities occur, which in turn generate new knowledge (i.e., these are essentially knowledge *outputs* of the QRM process) where gaps in knowledge (i.e., "known-unknowns") are identified, for which further study can be planned.

Continuing through the cycle, Node 4 represents the opportunity to increase knowledge as new knowledge is acquired, captured, and retained. This new knowledge is then managed via a series of KM practices, at Node 5. These KM practices (e.g., standardized KM methods and tools) ensure knowledge is managed as an asset, and made visible and available at Node 6. The purpose of Node 6 is to ensure that a company can apply the best of what it knows to facilitate continual improvement and well as continued or new QRM activities, at which point the cycle repeats. These nodes are intended to be sequential in nature. However, there is no fixed starting point in this overall process – Node 1 is not the only place to initiate the cycle. The cycle can and should be initiated at any of the nodes, based on the context at hand (e.g., new process knowledge may become available based on an investigation), as will be illustrated in the next section of this paper.

The remainder of this paper illustrates using case studies the practical application of the *RKI Cycle* and its associated concepts to parts of two product lifecycle phases – *Commercial Manufacturing* and *Technology Transfer*. In relation to *Commercial Manufacturing,* we illustrate the application of the *RKI Cycle* by focusing on change management activities and on the various triggers that can initiate the *RKI Cycle* at Nodes 1, 3, 4, and 6. With regard to *Technology Transfer*, which is often one of the most significant changes during the product lifecycle, we illustrate the application of the *RKI Cycle* at Node 5, titled *Manage Knowledge via KM Practices,* with a focus on the transfer of tacit knowledge. Node 2, titled *Manage Risk via the QRM Processes,* is probably the best characterized of all the nodes, in

particular due to the extensive guidance that is provided in ICH Q9 [2] on this topic, and so it is not specifically explored in this paper.

3 Application of the RKI Cycle to Commercial Manufacturing

Commercial Manufacturing is typically the longest stage of the Pharmaceutical Lifecycle and as such provides an abundance of opportunities for knowledge capture, flow, and management across numerous activities. ICH Q10 lists four PQS elements that are substantially dependent on the application of QRM and KM; these are *Process Performance and Product Quality Monitoring*, *Corrective Action/Preventive Action* (CAPA), *Change Management,* and *Management Review of Process Performance and Product Quality* [1]. Effective Change Management is central to the achievement of one of the objectives of ICH Q10 – continual improvement. Thus, it was selected as an appropriate element to illustrate the application of the *RKI Cycle*, as it is the element that is typically the most standard across companies, operations, and lifecycle.

The triggers for Change Management may vary – as described in the recent PIC/S Recommendation paper on *How to Evaluate/Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management* [7], which lists examples of potential triggers (or reasons to raise a Change Proposal), as follows[1]:

- *"upgrades to equipment or facilities*
- *improvements in raw materials*
- *improvements in manufacturing performance and consistency (to reduce variability, improve yield, etc.)*
- *enhancements in manufacturing capacity*
- *corrections of quality issues*
- *addressing signals from the PQS such as deviations, complaints/adverse events, corrective action and preventative action (CAPA), product quality review, operational review metrics, management review, new regulations, compliance gaps*
- *implementing innovation or continual improvement initiative"*

The list above gives a diverse range of reasons for proposing or triggering a change. Some of those will be evidence-based, supported by existing process and product knowledge. However, others, particularly those proposing new or innovative changes, may have a level of uncertainty and, consequently, will rely more on QRM for successful outcomes [8]. At a practical level, these differences mean that the change proposals can commence at different nodes in the *RKI Cycle*.

An *improvement* to manufacturing performance, or a preventive action, or a raw material improvement, are all triggers likely to be supported by a (statistically) significant volume of evidence-based data and/or explicit knowledge – gathered and systemized over time. This knowledge supports the proposed change and offers a high degree of certainty that it will be effective, and hence successful. This represents the

[1] The PIC/S document did not intend this to be a definitive or exhaustive list.

use of knowledge as a *change agent*. It is an input to the change and, as previously established, when this knowledge is applied, the risk of failure is reduced.

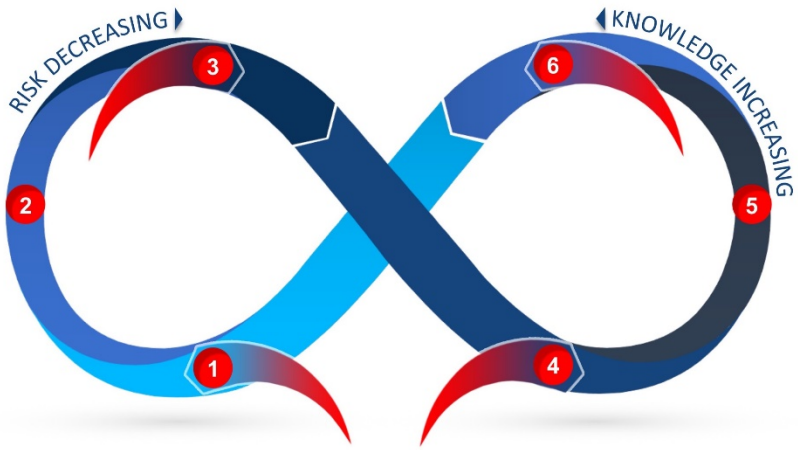
The only remaining concern is that of an *"unintended deleterious impact on product quality*," as highlighted in Chapter 1 of the EU GMP Guide [9]. This potential outcome must always be considered when implementing a change, irrespective of one's confidence level, and both KM and QRM can assist with this evaluation.

In contrast, a change proposal triggered to implement a *Corrective Action*, i.e., in response to an issue, usually involves a different starting point in the RKI Cycle. Typically, this type of change proposal is the consequence of an unforeseen failure of a risk control, or the absence of a required risk control. As this event was unforeseen, it likely represented a lack of knowledge or understanding, or it may have been a failure to recognize a changed circumstance. The risk control failure (or absence) will be investigated, resulting in new knowledge, and a change is proposed to re-establish control. When implementing change in these circumstances, there is typically some residual uncertainty remaining until, through monitoring and the collection of data and knowledge, control is re-established and confirmed. The risk of recurrence is, thus, reduced. This information becomes systemized as new knowledge, and it informs the *RKI Cycle*.

Other changes may be triggered by proposals to introduce *new and innovative technologies*. While some explicit or Subject Matter Expert (SME) knowledge will usually accompany such change proposals, there will usually be a lack of tacit knowledge within the organization in connection with such technologies. These types of changes also have a level of risk and uncertainty until the change is implemented and the applied controls are verified with real world data.

The above describes how the *RKI Cycle* need not start at the same point for different change proposals, and different change proposals may enter the *RKI Cycle* at different entry points. This paper proposes four potential entry points based on different triggering factors (as depicted in Figure 3.1 [10]) as a means to illustrate application of the RKI Cycle.

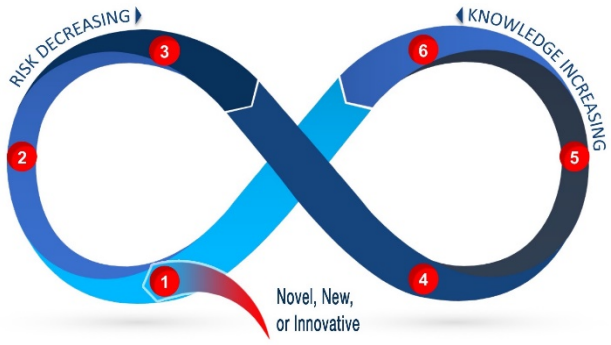
Figure 3.1: Potential Entry Points for the RKI Cycle [10]



Case Study 1

Novel, New, or Innovative Changes:

Entry at Node 1



A change enters at the earliest point in the RKI Cycle. This is the entry point for anything *new, novel, or innovative*. This is because, while the change proposal will be supported by a certain amount of information, probably of external origin, there will usually be a deficit of tacit knowledge about the "to-be" process within the organization, leading to uncertainty and risk. The impact on the current and future states must be fully understood in order to approve the change and to have a controlled implementation plan. The change proposal must be supported by a quality risk management process to identify the hazards, understand their significance, and establish the correct risk controls. This requires the application of the complete RKI learning cycle, starting with knowledge-driven risk assessments, where knowledge is an input to those risk assessments.

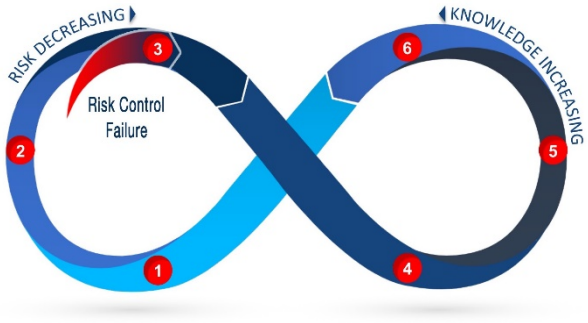
Example: Company X identifies an improvement opportunity based on changing an in-process test method. The "new" method will reduce the cycle time between sampling and result. The proposed method is an established technology in other industries. Therefore, there is a volume of literature on its application, and the supplier of the technology can supply training and technical support. However, it is "new" to this operation and process. There is concern whether the data produced by the new technology will be readily interpretable with respect to product and process control, and whether the higher sensitivity of this technology will result in unknown outcomes and unforeseeable results. These are uncertainties that represent real hazards and concerns.

In this case, the change proposal should be treated with the full *RKI Cycle,* from the initial starting point (Node 1). QRM will establish the hazards and risks that must be controlled. It will evaluate the likelihood of those hazards occurring, the risk levels associated with them and the appropriate controls and/or responses. Any concerns or uncertainties that are deemed to be unacceptably high will require further research or off-line studies to resolve. (Nodes 1-3 on *RKI Cycle.*) The change proposal, when approved, will be implemented with a supporting implementation and monitoring plan to ensure that knowledge and understanding are gained, evaluated, and used to refine or improve the implementation plan, where necessary. (Nodes 4-6 on the *RKI Cycle*)

Case Study 2

A Risk Control Failure:

Entry at Node 3



Node 3 is the entry point for when a *risk control has failed or is absent*, e.g., a non-conformance is detected, a detection control has missed a defect, there is no risk control in place for a hazard that has come to light, etc. The issue has been investigated resulting in CAPA actions, some of which require a change proposal to implement them. The state of knowledge has changed - new knowledge has introduced a "known-unknown," which needs to be fully understood in order to assess and determine the appropriate "new" risk control strategy. The organization must determine how to gain the knowledge required to support an assured approach (Nodes 3-6 on the *RKI Cycle*). This new information will then be used to re-assess the quality risk management strategy through a revised QRM evaluation process. (Nodes 1-3 on the *RKI Cycle*)

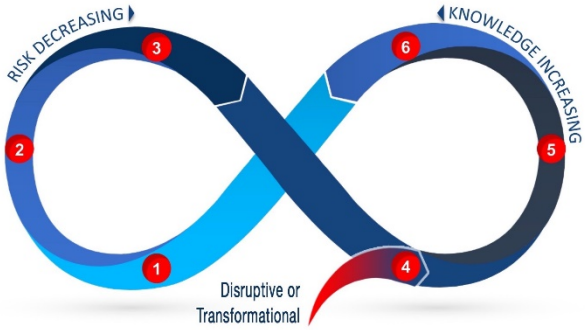
Example: In Company X, QC testing reveals a change in the color of an API manufactured at the site. It is more "yellow" than the specification of "white to off-white." While API color may not be considered a patient-critical attribute, API appearance is regarded as a Critical Quality Attribute (CQA) and the out-of-specification test result must of course be investigated to determine its root cause(s). (The purity of the API material is in doubt, and also, an off-color finished product (a solution for injection in this case) could be considered to be contaminated.) The root cause analysis reveals that one of the starting materials used in the manufacture of the failing API lot was within specification for color but trending high. The relationship between this starting material attribute and the appearance CQA of the API was not previously understood. Laboratory experiments using starting material of different color ranges confirmed the cause-effect. This is new knowledge. The change proposed is to tighten the color specification applied by Company X to the starting material. The starting material is an off-the-shelf chemical manufactured and supplied by a major chemical supplier, and getting that company to agree to tighten its own specification for the material is not an option. (This would involve Nodes 3-6 on the *RKI Cycle*.)

The tightened specification at Company X will likely result in the rejection of some lots of the starting material, and this may well introduce risks to the supply chain and manufacturing planning activities. These potential risks must be understood and assessed through QRM, to determine an appropriate risk control plan. (Nodes 1-3 on the *RKI Cycle*)

Case Study 3

Introducing a Disruptive or Transformational Technology:

Entry at Node 4



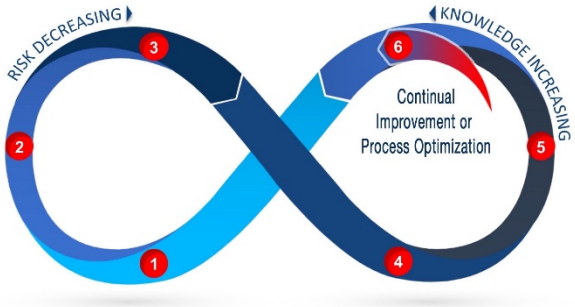
In this case study, the change represents introduction of a pioneering disruptive or transformational technology to a site. While the introduction of continuous manufacturing or automation might be the obvious type of change in this category, these are typically large projects and are often managed at a higher level than just the site change management system, although the latter will certainly be involved.

Example: In Company X the application of a bespoke robotic technology to a process step is proposed. While the technology itself is understood and widely used outside the organization, the return on investment and the benefits accrued by applying it are unclear. Also unclear is the amount and type of in-house support required to operate and maintain the equipment. There are also concerns in relation to reliability and down-time. These are all "unknowns" associated with the project and these knowledge gaps must be filled before the viability of the proposal can be considered. These will need further research and possibly some pilot scale projects to build a knowledge base on which the proposal can be truly evaluated (Nodes 4-6 on the *RKI Cycle*). Doing this will provide some useful information, but the true benefits of installing the technology will not be fully understood until it is applied to the process; thus there is risk that must be evaluated through QRM (Nodes 1-3 on the *RKI Cycle*).

Case Study 4

Continuous Improvement or Process Optimization:

Entry at Node 6



A recent research survey exploring the benefits of the *RKI Cycle* [6] suggests that there often are knowledge repositories and databases which are not analyzed systematically for opportunities to propose improvements or to optimize processes, even though this is advocated by ICH Q10.

Integration of this "analysis lens" into existing reviews, such as annual product quality reviews or management reviews, might systemize the opportunity to create these change proposals. Certainly, the opportunities are enhanced when KM, as a practice, is well integrated across the pharmaceutical quality system.

Examples of *continual improvement or process optimization changes,* as cited in the aforementioned PIC/S paper [9] include enhancements to reduce process variability or to improve yield. For such change proposals, a body of reliable evidence will usually have been built up over time, the process may be relatively well understood, and an analysis of the change proposal may indicate a high level of confidence in a positive outcome. These change proposals can also represent a cost reduction opportunity, which is data driven but which also represents a potential increase in risk control. These changes, supported by a body of evidence and both explicit and tacit knowledge, would enter at Node 6 on the *RKI Cycle*.

Example: Company X has a proposal to reduce the frequency of samples tested on an incoming material from a trusted supplier. While the historical evidence (Node 4 on the *RKI Cycle*) indicates that the risk is low, this data must be analyzed in the context of the proposal (Node 6 on the *RKI Cycle*) and the impact on the overall state of risk control must be understood via QRM activities (Nodes 1-3 on the *RKI Cycle*). A potential outcome is that the level of residual risk may not be accepted and the frequency of sampling remains as is.

As these four cases studies illustrate, systemizing the acquisition of knowledge, in particular tacit knowledge, allows for more informed decision-making in the change management system. The need to effectively manage knowledge applies throughout the Commercial Manufacturing stage of the product lifecycle, and the management of risk is continuously strengthened by the acquisition and application of new knowledge. The *RKI Cycle* provides a sustainable foundation for an effective PQS, where KM and QRM are not considered separate enablers, but as an intertwined enabler, working together synergistically and continuously – each one benefiting from the other.

4 Application of the *RKI Cycle* to Technology Transfer

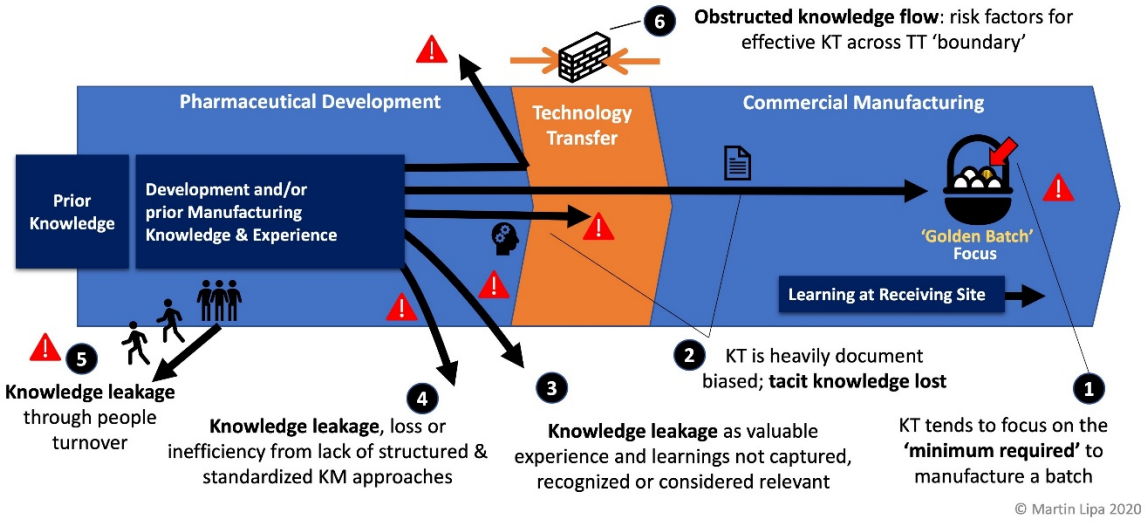
Research has shown that *explicit* and *tacit* knowledge are considered critically important to efficient and effective technology transfer [11]. However, it was found that while the transfer of *explicit* knowledge was considered to be marginally effective, (i.e., transfer of documents and other codified information), the transfer of *tacit* knowledge (e.g., know-how, insights, decision rationale, history ideas), was considered to be *somewhat ineffective*.

In examining the application of the *RKI Cycle* to *Technology Transfer*, Node 5 is of particular interest given the relative immaturity of KM in the pharmaceutical industry [12], and given that it is only through effective KM that much of the knowledge transfer associated with technology transfer can effectively occur in a robust and consistent manner. Furthermore, given the general ineffectiveness of tacit

knowledge transfer, case studies which highlight methods for tacit knowledge transfer are important. Two illustrative case studies are presented later in this paper.

Figure 4.1 depicts a visual representation of the challenges to knowledge transfer during technology transfer. The figure shows how knowledge can sometimes fail to successfully transfer into commercial manufacturing, as depicted by the arrows indicating knowledge "flow." Knowledge may "leak" or otherwise be obstructed as suggested by a series of failure modes (represented by red triangles).

Figure 4.1: Knowledge Transfer Challenges during Technology Transfer



These failure modes noted as (1) to (6) are described as follows (adapted from Lipa et al [13]):

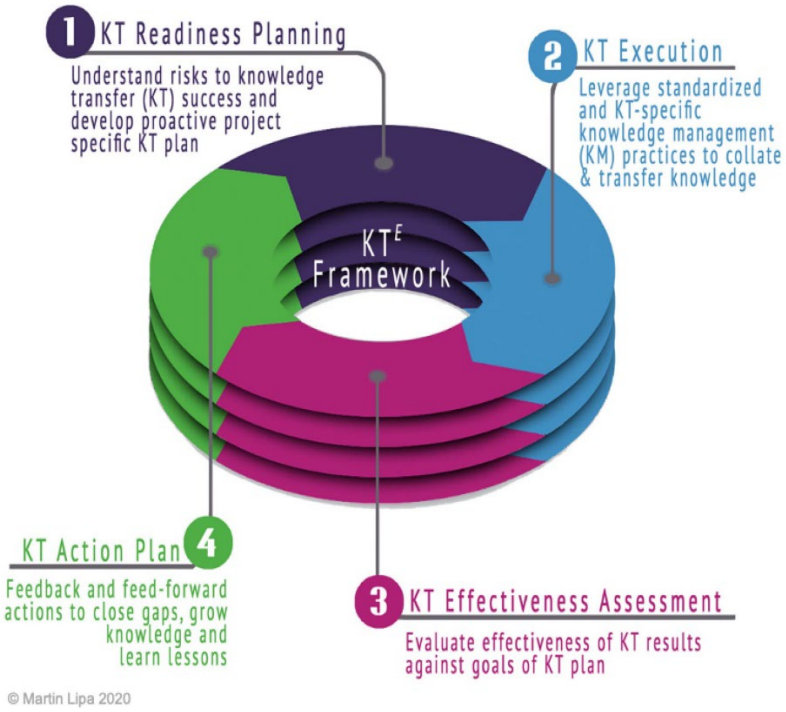
1. Knowledge transfer tends to focus on the "golden batch" which is often regarded as the "minimum required" by the receiving site to successfully manufacture the product. The focus tends to be on transferring the knowledge required for "what goes right." Knowledge associated with "what goes wrong" is often not transferred.
2. Knowledge transfer is typically focused on document transfer (i.e., explicit knowledge). While some tacit knowledge[2] transfer activities occur on an ad hoc basis (e.g., staff at the receiving unit witnessing a batch being manufactured at the sending unit), these attempts at tacit knowledge transfer tend to be unstructured and highly variable in approach. Therefore, while explicit knowledge may be transferred to the receiving unit, often valuable tacit knowledge is not transferred and may be lost.
3. Knowledge leakage can occur when valuable experience and learnings are not captured, recognized, or considered relevant.
4. Knowledge leakage can also occur from a lack of structured and standardized KM methods and tools.

[2] Tacit knowledge is commonly described as "know how," experience, decision rationale, and other non-codified knowledge "in the heads of people."

5. Knowledge leakage can also occur from staff turnover and the loss of tacit knowledge held by individuals.
6. Obstructions to knowledge flow can be present. These can be due to certain knowledge transfer barriers between pharmaceutical development and commercial manufacture during technology transfer activities. Such barriers can relate to process complexity, low staff competency at the receiving site, differences in time zones, language issues, cultural differences, etc.

To address these challenges, Lipa et al in 2020 developed a 4-step framework to standardize and improve knowledge transfer, known as the *Knowledge Transfer Effectiveness* Framework (KT^E), shown below in Figure 4.2 [14].

Figure 4.2: The KT^E Framework [14]



The steps of the KT^E Framework, which represent a continual improvement cycle of *'plan, do, check, act'* in action are as follows:

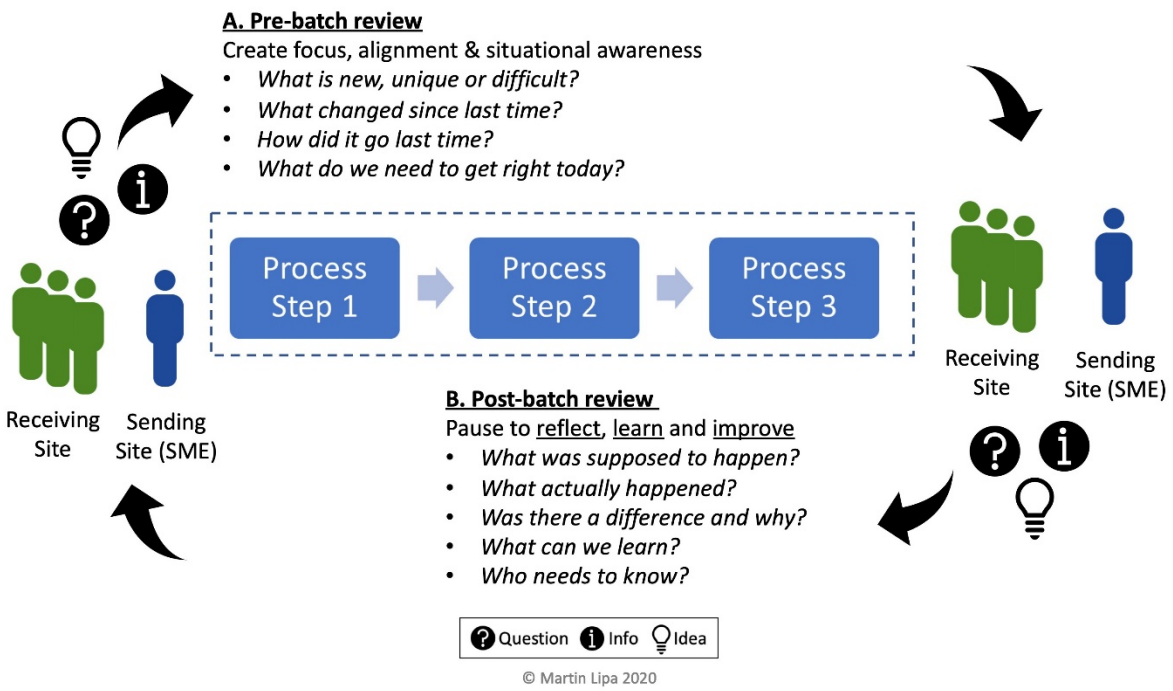
1. **KT Readiness Planning:** Assess risk and create a proactive knowledge transfer plan
2. **KT Execution:** Execute an effective knowledge transfer by using standardized and technology transfer-specific KM methods and tools
3. **KT Effectiveness Assessment:** Assess the effectiveness of knowledge transfer, relative to the knowledge transfer plan
4. **KT Action plan:** Capture lessons learned and take action to close gaps

Each of the four steps are supported by a respective toolkit [13], which contains a series of methods and tools such as standard KM practices, templates, checklists, etc., and which provide the necessary structure for enhanced knowledge transfer.

The following case studies illustrate simple methods to facilitate the transfer of tacit knowledge [15], both of which represent tools within the **KT Execution** portion of the above KT^E Framework.

Case Study 5

Facilitating Tacit Knowledge Transfer through Pre-batch and Post-batch Reviews

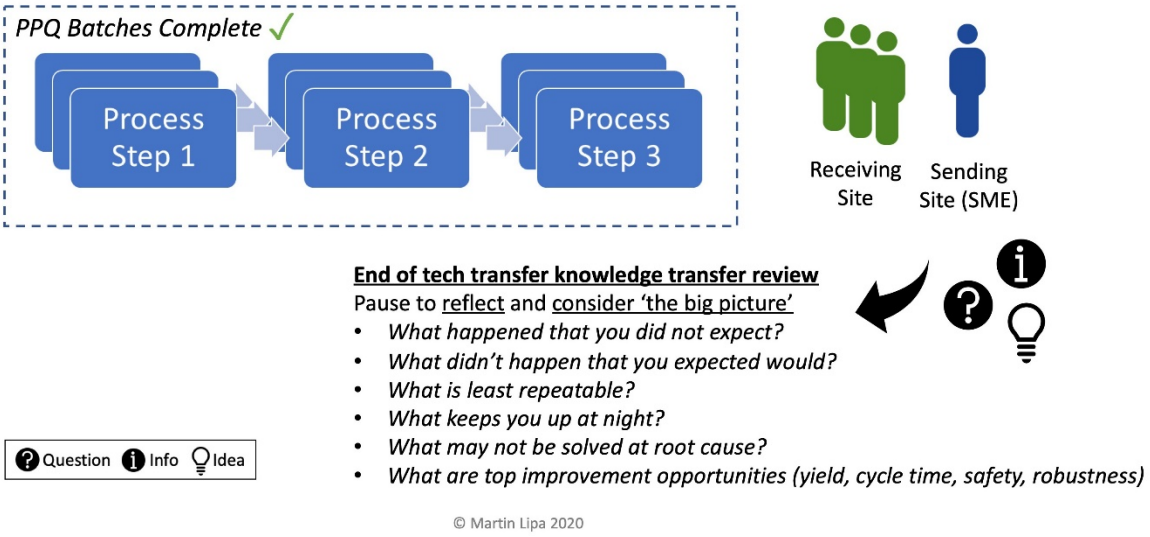


The case study [15], which was based on validation batches during technology transfer of a multivalent vaccine, started with a *pre-batch review* with the receiving site team and sending site SME to the receiving site. The process included a review of structured, open-ended questions which created context and dialogue to review the upcoming tasks at hand. This process took knowledge (e.g., assumptions) that might be obvious to an expert but not to others, and created a dialogue with the receiving site, allowing valuable learnings to be shared, as well as creating alignment and situational awareness for the team. Once the batch was completed, a *post-batch review* was carried out, which followed a traditional "after-action" approach designed to reflect, learn, and improve. Again, a series of pre-planned questions were posed to explore learning opportunities, and governance was in place to ensure that lessons were in fact learned by tracking their implementation.

In this case study, 82 potential actions flowed from the paired reviews, which led to 52 proactive actions having been taken. More importantly, as a result of those proactive actions, an estimated 43 potential deviations had been avoided, demonstrating improved "right first time" process execution.

Case Study 6

Facilitating Tacit Knowledge Transfer through Post-validation Review



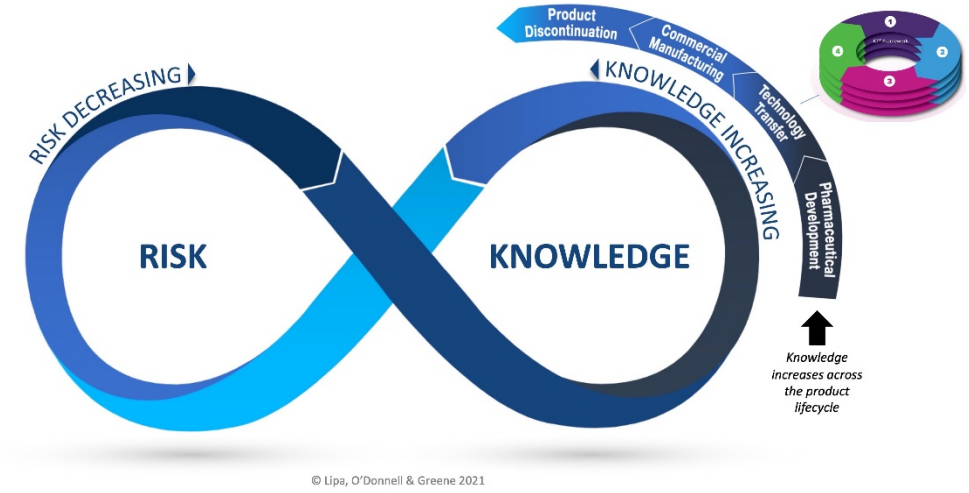
A second case study [15] focused on a review which took place at the end of the Process Performance Qualification (PPQ) batches, and which had been designed to pause and *reflect on the "big-picture."* A set of open-ended, reflective questions was posed (e.g., *What didn't happen that you expected would? What is least repeatable?*).

While not an elaborate process, this simple reflection generated rich dialogue and created a conversation that did not just help transfer knowledge, it increased product and process understanding at the receiving site in a way that would not have typically happened. Feedback from the receiving site was highly positive – the exercise was seen as an investment in capability building that would help with the receiving site's ability to troubleshoot problems and prevent repeat mistakes, while improving overall process robustness.

In this case study, 70 responses to the various questions were captured. This led to 39 proactive actions being taken to enhance the transfer of history, ideas, improvement suggestions, and helped explore rationale and risks.

In this application of the *RKI Cycle* to *Technology Transfer*, the KT^{E} Framework – inclusive of the associated toolkit of KM practices – serves as a solution for "how" knowledge is effectively managed during technology transfer (Figure 4.3). Such knowledge is then available for the later stages of the product lifecycle, in particular *Commercial Manufacturing,* where not having that knowledge can be very disabling, leading to increased risks, reworks, potential supply disruptions, and a variety of other undesirable conditions.

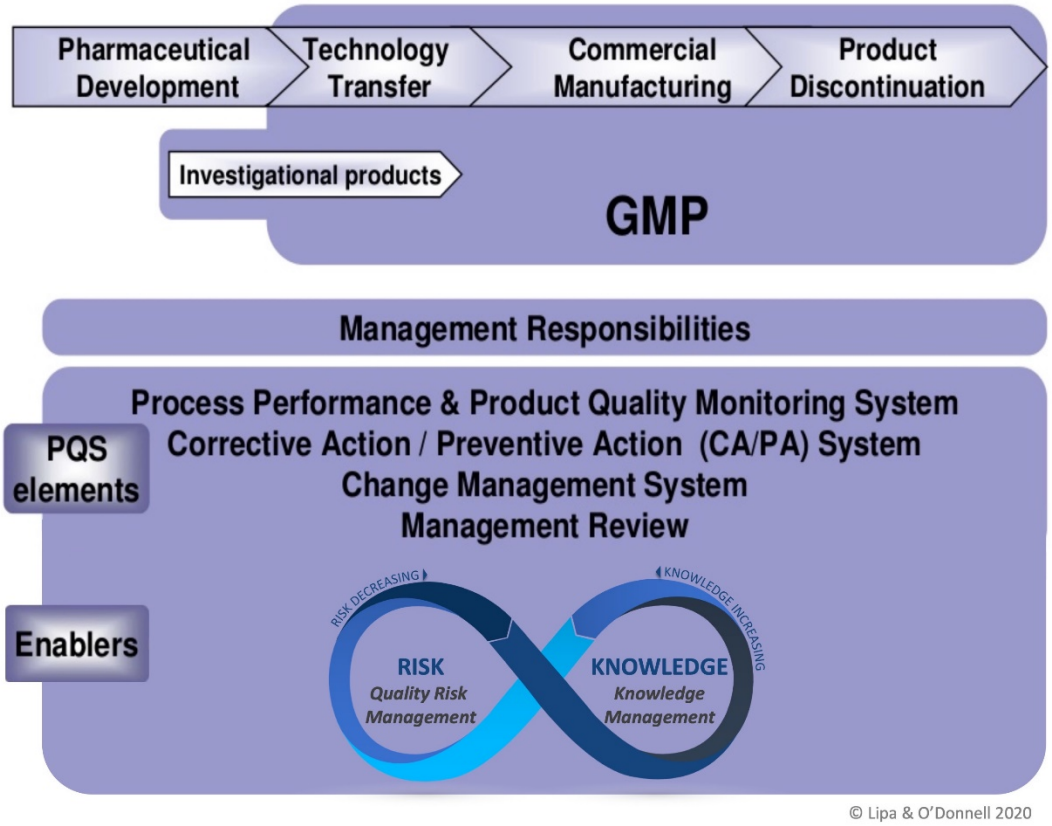
Figure 4.3: KTE as the "How" for KM during Technology Transfer



5 Conclusion

The concepts presented in this paper transcend the entire PQS, from "top to bottom" across the four PQS elements, and from "left to right" across the four phases of the pharmaceutical product lifecycle. There are clear expectations prevalent in ICH Q10 and throughout regulatory and industry guidance [3] that risk and knowledge be considered interdependent, to ensure use of the best available product and process knowledge, so that the most timely, most informed, and most-evidence-based decisions can be made. Yet while there is evidence that the pharmaceutical industry recognizes this interdependency, the available indicators are that the industry is far from achieving this connection in practice [6]. A re-imagined foundation for the PQS, as illustrated in Figure 5.1 below and which explicitly demonstrates the expected connection between QRM and KM as co-enablers to an effective PQS, is a helpful means to visualize this opportunity [4].

Figure 5.1: A Re-imagined Foundation for the PQS [4]



The 'transitional' nodes in the *RKI Cycle* between QRM and KM (i.e., Nodes 1, 3, 4 and 6 from Figure 2.2) help provide cohesion of QRM and KM by defining an integrated and cyclical process in a stepwise fashion, where an organization continually seeks to maximize knowledge and minimize risk. Without these nodes connecting the formal QRM and KM activities (Nodes 2 and 5), QRM and KM are likely to revert back to independent and disconnected PQS enablers.

The *RKI Cycle*, along with the cases studies presented in this paper for *Commercial Manufacturing* and *Technology Transfer*, provides a tangible means to improve one's understanding and recognition of the importance of the QRM-KM interdependency, and how this interdependency can be immediately made real.

Disclaimer

The views expressed in this article are those of the authors and are not necessarily those of the Health Products Regulatory Authority (HPRA).

References

1. ICH, *Pharmaceutical Quality System Q10*. Geneva, 2008.
2. ICH, *Quality Risk Management Q9*. Geneva, 2005.
3. M. J. Lipa, K. O'Donnell, and A. Greene, "Managing Knowledge and Risk - A Literature Review on the Interdependency of QRM and KM as ICH Q10 Enablers," *Journal of Validation Technology (JVT)*, vol. 26, no. 4, 2020.
4. M. J. Lipa, K. O'Donnell, and A. Greene, "Knowledge as the Currency of Managing Risk: A Novel Framework to Unite Quality Risk Management and Knowledge Management," *Journal of Validation Technology (JVT)*, vol. 26, no. 5, 2020.
5. M. J. Lipa and P. Kane, "Mapping KM Methods and Tools across the Pharmaceutical Product Lifecycle," *Level3*, vol. 15, no. 2, 2021.
6. M. J. Lipa, K. O'Donnell, and A. Greene, "A Survey Report on the Current State of Quality Risk Management (QRM) and Knowledge Management (KM) Integration," *Level3*, vol. 15, no. 3, 2021, [Online]. Available: https://arrow.tudublin.ie/level3/vol15/iss3/5/.
7. PIC/S, "How to Evaluate / Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management (PI 054-1)," 2019. [Online]. Available: www.picsheme.org.
8. V. Mulholland and A. Greene, "Quality Risk Management: Seeking the Diamonds: Making the Case for Improved Formality in QRM Decision-making," *Level3*, vol. 15, no. 2, p. 18, 2020, [Online]. Available: https://arrow.tudublin.ie/level3doi:https://arrow.tudublin.ie/level3/vol15/iss2/18/Availableat:https://arrow.tudublin.ie/level3/vol15/iss2/18.
9. 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*, 2012.
10. Pharmaceutical Regulatory Science Team, "Risk-Knowledge Infinity Cycle," 2021. https://prst.ie/rkicycle/ (accessed Apr. 06, 2021).
11. M. J. 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.
12. P. Kane, "A Blueprint for Knowledge Management in the Biopharmaceutical Sector," 2018.
13. M. J. Lipa, A. Greene, and N. Calnan, "Knowledge Management as a Pharmaceutical Quality System Enabler: How Enhanced Knowledge Transfer Can Help Close the ICH Q10 to ICH Q12 Gap," *PDA journal of pharmaceutical science and technology*, vol. 75, no. 1, pp. 64–90, 2021, doi: 10.5731/pdajpst.2020.011825.
14. P. Kane and M. J. Lipa, *Advancing Knowledge Management (KM) as an ICH Q10 Enabler in the Biopharmaceutical Industry*. Dublin: TU Dublin Academic Press, 2020.
15. M. J. Lipa, P. Kane, and A. Greene, "Simple Practices to Facilitate the Flow of Valuable Tacit Knowledge during Biopharmaceutical Technology Transfer: A Case Study," *Level3*, vol. 15, no. 2, 2020.