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Unlocking Knowledge to Benefit the Patient: How Connecting KM and QRM Can Strengthen Science and Risk-Based Decision Making

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A thesis submitted to Technological University Dublin in fulfilment of
the requirements for the award of Doctor of Philosophy (PhD)

Supervisors: Professor Anne Greene & Dr Nuala Calnan

May 2021

Abstract

This thesis explored knowledge management effectiveness in the pharmaceutical sector and included an examination of the critical relationship between knowledge management (KM) and quality risk management (QRM) as the dual enablers of an effective pharmaceutical quality system. The primary research objectives were to improve understanding and effectiveness of the interdependency between KM and QRM and to improve knowledge management across the pharmaceutical product lifecycle, starting with a focus on knowledge transfer during technology transfer. The thesis explored how improved KM across the product lifecycle coupled with thoughtful and intentional connectivity between KM and QRM as defined by this study could lead to more informed risk-based decision making and ultimately help benefit patients.

This research study employed a variety of methods, including literature review, expert interviews, philosophical dialogue, focus groups, and case studies as a means to include a large number of stakeholders across the pharmaceutical sector. The study progress was disseminated through a variety of methods and channels including several peer-reviewed papers and conference presentations as a means to solicit input and feedback.

The research findings verify that while KM and QRM are considered highly interdependent in theory, in practice they are – at best – partially integrated. This suggests the industry is not leveraging the best knowledge available to inform QRM, leading to sub-optimal risk-based decision making. Furthermore, knowledge created during QRM activities may not be effectively managed.

When considering technology transfer, the study found that while knowledge transfer is considered critically important, knowledge transfer is only *marginally effective* for explicit knowledge and *somewhat ineffective* for tacit knowledge. This lack of effective knowledge transfer poses a risk to successful technology transfer and the goals of ICH Q10.

In response to these findings, the research generated a variety of outputs, many of which have already demonstrated outcomes and impacts on the sector and have the potential for seminal importance. These outputs include a *Knowledge Management Process Model* to define the process of knowledge management, the *Risk-Knowledge Infinity Cycle (RKI Cycle)* as a framework to unite KM and QRM, a framework for knowledge transfer enhancement (*KT^E Framework*) during technology transfer, and a variety of case studies to demonstrate the impact of these outputs and their applicability across the product lifecycle.

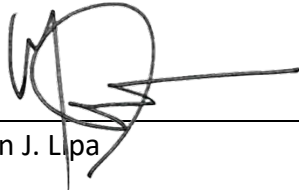
These outputs can be immediately applied to the benefit of the pharmaceutical sector. Areas of future study include additional assets such as training and application materials to accelerate application of these outputs. Additional opportunity also exists to better define knowledge transfer toolkits, create knowledge management frameworks for other phases of the product lifecycle, and to better define the relationship between data analytics, knowledge management and risk management.

Declaration

I certify that this thesis which I now submit for examination for the award of Doctor of Philosophy (PhD), is entirely my own work and has not been taken from the work of others, save and to the extent that such work has been cited and acknowledged within the text of my work.

This thesis was prepared according to the regulations for graduate study by research of the Technological University Dublin and has not been submitted in whole or in part for another award in any other third level institution. The work reported on in this thesis conforms to the principles and requirements of the TU Dublin's guidelines for ethics in research.

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Martin J. Lipa

06 - MAY - 2021

Date

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To all those who participated in this research, thank you for your insights and feedback to give this research study meaning in this time of rapid and unprecedented change.

To my parents, the only thing bittersweet about this milestone is that you were not here to enjoy it with me. You have each done so much for me – thank you – and I miss you.

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Glossary of Terms and Abbreviations

Term	Definition
AMT	Analytical Method Transfer
API	Active Pharmaceutical Ingredient
APQC	American Productivity & Quality Center, a member-based knowledge management organisation
APR	Annual Product Review
ATMP	Advanced Therapy Medicinal Products
CAGR	Compound Annual Growth Rate
CAPA	Corrective Action Preventative Action
CMC	Chemistry, Manufacturing & Controls
CMO	Contract Manufacturing Organisation
CoE	Centre of Excellence
Cpk	Process Capability
CQA	Critical Quality Attribute
CRADA	Cooperative Research and Development Agreement
CTQ	Critical to Quality
DCOM	Direction, Competency, Opportunity, Motivation
DMADV	Define-Measure-Analyse-Design-Verify
DMAIC	Define-Measure-Analyse-Improve-Control
E2E	End-to-end
EU	European Union
FDA	United States Food and Drug Administration (US regulatory agency)
FMEA	Failure Mode Effects Analysis
GMP	Good Manufacturing Practice
GxP	'Good Practice' quality guidelines and regulations (where 'x' is a variable (e.g., 'M' = 'Good <i>Manufacturing</i> Practices', L = Laboratory, D = Documentation, C = Clinical))
HOKE	House of Knowledge Excellence
HPRA	Health Products Regulatory Authority (Ireland regulatory agency)

Term	Definition
ICH	International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q8	ICH Guideline on <i>Pharmaceutical Development</i>
ICH Q9	ICH Guideline on <i>Quality Risk Management</i>
ICH Q10	ICH Guideline on <i>Pharmaceutical Quality System</i>
ICH Q11	ICH Guideline on <i>Development and Manufacture of Drug Substances</i>
ICH Q12	ICH Guideline on <i>Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management</i>
ICH Q14	ICH Guideline on <i>Analytical Procedure Development (guideline in development)</i>
IEC	International Electrotechnical Commission (an international standards organisation that prepares and publishes international standards for all electrical, electronic, and related technologies)
ISO	International Organisation for Standardisation
ISPE	International Society for Pharmaceutical Engineering
KM	Knowledge Management <i>These terms will be used interchangeably throughout this thesis based on context</i>
KPI	Key Performance Indicator
KT	Knowledge Transfer
KT^E	Knowledge Transfer Enhancement
MHRA	U.K. Medicines and Healthcare products Regulatory Agency
MSD	Merck Sharp & Dohme
NASA	National Aeronautics and Space Administration (US Space Agency)
NPI	New Product introduction
ONA	Organisational Network Analysis
PAC	Post-Approval Change
PDA	Parenteral Drug Association
PDCA	Plan-Do-Check-Act
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMTc	Pharmaceutical Manufacturing Technology Centre
PPKL	Pharmaceutical Product Knowledge Lifecycle

Term	Definition
PPQ	Process Performance Qualification
PQR	Product Quality Review
PQS	Pharmaceutical Quality System
PRST	Pharmaceutical Regulatory Science Team (a research body at Technological University Dublin)
Q&A	Questions & Answers
QbD	Quality by Design
QRM	Quality Risk Management <i>These terms will be used interchangeably throughout this thesis based on context</i>
RAQAB	Regulatory Affairs and Quality Advisory Board of PDA
RM	Risk Management
SIPOC	Supplier-Input-Process-Output-Customer
SME	Subject Matter Expert
TT	Technology Transfer
TU Dublin	Technological University Dublin
WHO	World Health Association

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Thesis Overview

This thesis has been organised into four parts across 12 chapters as a means to summarise the important contributions of the associated research study as outlined below. Significant findings from the research were disseminated through a series of peer-reviewed papers in a variety of journals which enabled socialisation and feedback on research progress during the study. These papers are referenced appropriately throughout this thesis.

Part One lays the foundation for this research study, including relevant background and context. A literature review examines expectations for managing knowledge and risk, the interdependency of Knowledge Management (KM) and Quality Risk Management (QRM), and reviews recent developments in KM. It further explores relevant regulatory and industry guidance on technology transfer and knowledge management and profiles related research by the Pharmaceutical Regulatory Science Team (PRST) at the Technological University Dublin (TU Dublin).

Part Two examines the relationship between knowledge and risk. It explores the opportunity to better integrate KM and QRM. In response to the findings of this examination, potential solutions are provided through a proposed *Knowledge Management Process Model*, the *Risk-Knowledge Infinity Cycle (RKI Cycle) Framework* to integrate KM and QRM, and the *KT^E Framework* as a means to enhance knowledge transfer during technology transfer.

Part Three demonstrates how the *RKI Cycle* can be applied across the product lifecycle, including three examples with a focus on each KM across the product lifecycle, change management during commercial manufacturing, and the link between QRM, KM and data analytics. This part also explores the concept of *knowledge culture*, including a review of current cultural issues which are barriers to knowledge management in the pharmaceutical industry, existing definitions of knowledge culture outside of the

pharmaceutical industry, and benchmarking the corollary of *quality culture*. This section concludes with proposing a preliminary ‘ideal knowledge culture.’

Part Four brings the research study to a close with a review of the outputs, outcomes, and impact of this research study, followed by conclusions and opportunities for future research.

The following table (*Thesis Overview*) provides a chapter-level summary of the four parts of this thesis.

Thesis Overview

Part	Chapters
Part One: Research Study Foundations	<ul style="list-style-type: none"> • Chapter 1: Study Introduction and Context • Chapter 2: Literature Review • Chapter 3: Research Design, Methodology, and Methods
Part Two: Advancing KM and Developing QRM-KM Connectivity	<ul style="list-style-type: none"> • Chapter 4: A Process Model for Knowledge Management • Chapter 5: Re-Imagining the QRM-KM Interdependency • Chapter 6: The Opportunity to Improve Knowledge Transfer During Technology Transfer • Chapter 7: A Proposed Framework and Toolkit to Enhance Knowledge Transfer During Technology Transfer
Part Three: The <i>RKI Cycle</i> Across the Product Lifecycle and Knowledge Culture as a Catalyst	<ul style="list-style-type: none"> • Chapter 8: Demonstrating How the <i>RKI Cycle</i> can be Applied Across the Product Lifecycle • Chapter 9: Knowledge Culture as a Catalyst to Accelerate <i>RKI Cycle</i> Adoption and Impact
Part Four: Outcomes and Impact, Conclusions and Opportunities for Future Research	<ul style="list-style-type: none"> • Chapter 10: Outputs, Outcomes, and Impacts of this Research Study • Chapter 11: Conclusions to this Research Study • Chapter 12: Opportunities for Future Research

Part One: Research Study Foundations

Part One lays the foundation for this research study, including:

- Study introduction and context (Chapter 1)
- A literature review of a variety of relevant topics (Chapter 2), setting the stage for the managing of knowledge and risk to inform risk-based decision making and ultimately benefit patients
- An overview of the research methodology (Chapter 3)

Chapter 1: Study Introduction and Context

This thesis outlines a research study into Knowledge Management (KM) and Quality Risk Management (QRM) in the pharmaceutical sector^{1,2}. This study explored the current state of KM and QRM as dual enablers of an effective Pharmaceutical Quality System (PQS) and presented a framework for integrating them. It further examined the state of knowledge management across the product lifecycle³, with specific focus on technology transfer and the challenges associated with the identification and transfer of tacit knowledge.

The purpose of this opening chapter is to outline the intent and scope of the overall research study, define KM and its relevance within the pharmaceutical sector, preview the anticipated impact of this study, and introduce the researcher.

1.1 Purpose of the research and the problem addressed

The overarching goal at the commencement of this research study was to advance the understanding of KM within the pharmaceutical sector and encourage ways for it to be adopted more widely. There are many benefits associated with KM including operational effectiveness and employee engagement (Yegneswaran, Thien and Lipa, 2017), and the outputs of this thesis will further advance these impacts.

However, **the ultimate goal of this research was to provide tangible benefit to the patient by improving PQS effectiveness through meaningful advancement of KM as a PQS enabler**. As will be discussed later in this chapter and reinforced throughout this thesis, KM effectiveness in the pharmaceutical industry is lacking and the inter-relationship between KM and QRM is not well established. Yet, when organisations can apply their best knowledge, know-how, expertise, and experience – across boundaries

¹ The term “pharmaceutical sector” for the purpose of this thesis refers to the collective organisations involved in the product life cycle of a medicinal product (both chemical and biological entities) from discovery to patient, including industry, regulators, academia and related associations.

² For the purposes of this thesis, ‘biopharmaceutical’ and ‘pharmaceutical’ are considered synonymous, both terms are used interchangeably based on the source.

³ The product lifecycle is defined in ICH Q10, section 1.2 and includes the stages of pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation (ICH, 2008).

including organisational structures, geographies, and time – to support risk-based decision making, acceleration of product development through the use of prior knowledge, more robust processes, solving problems at root cause, and right-first time and on-time technology transfers – *the patient stands to benefit*. These patient benefits will include **increased product quality** (e.g., through reduced variability), **accelerated availability of new therapies, the potential to reduce drug shortages**, and more. Figure 1-1 illustrates this connection between the patient, the pharmaceutical regulations, the PQS as defined by ICH Q10 (ICH, 2008), and KM as an enabler to an effective PQS.

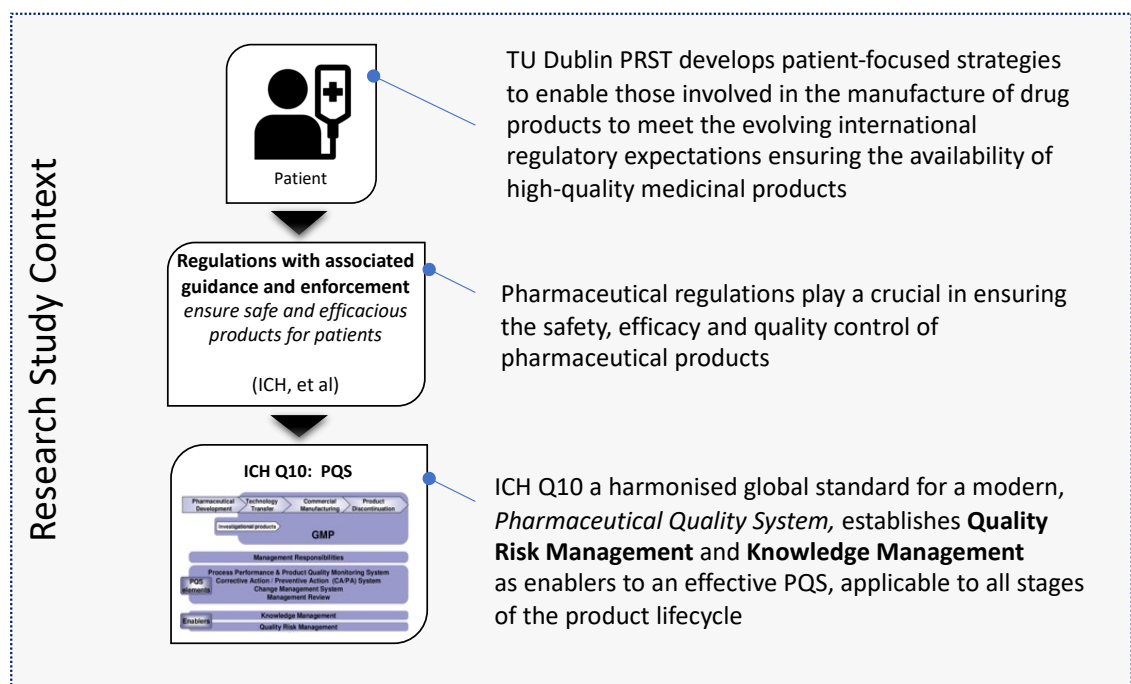


Figure 1-1 – The link between the patient, the regulations, the PQS, and KM as a PQS enabler

The researcher, as a member of the TU Dublin Pharmaceutical Regulatory Science Team (PRST), sought to improve KM competency and utilisation across the industry as a means to advance KM as an equally indispensable enabler to an effective PQS as QRM and unlock the aforementioned benefits.

1.2 Background on Knowledge Management and Quality Risk Management

In 2008, the International Council for Harmonisation (ICH)⁴ published the guideline *Pharmaceutical Quality System ICH Q10* (ICH, 2008), which described a model for an effective quality management system for the pharmaceutical industry, referred to as the Pharmaceutical Quality System, or PQS. In ICH Q10, knowledge management as a concept was cast into the mainstream of the pharmaceutical sector as it was positioned as a key enabler of an effective PQS, as depicted in Figure 1-2.

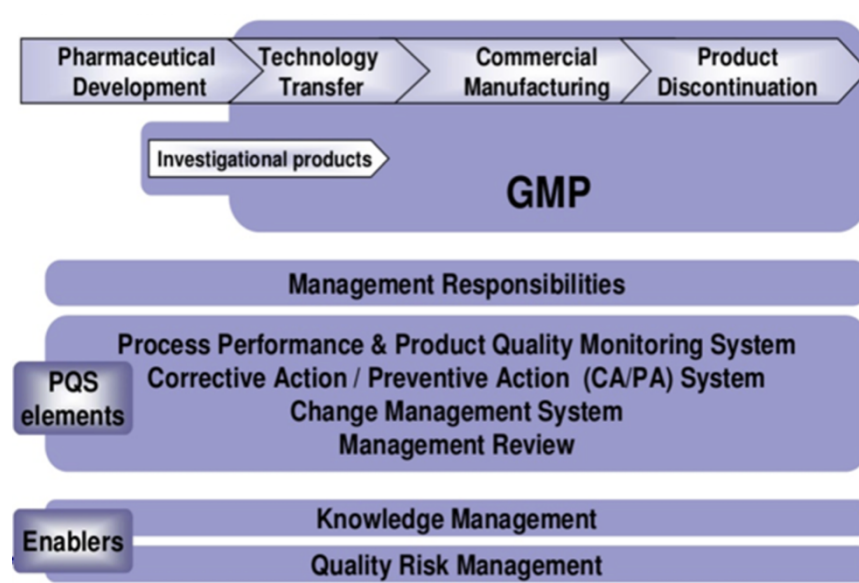


Figure 1-2 – The pharmaceutical quality system per ICH Q10 (ICH, 2008)

ICH Q10 defined KM as a ‘Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components’ (ICH, 2008). Additional definitions of KM are explored in Chapter 2 (section 2.1).

With KM and QRM positioned as key enablers for an effective PQS, the research study began with a literature review, evaluating the relationship between risk and knowledge. A key insight emerged from this review: **risk varies inversely with knowledge applied.**

⁴ The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner.

Therefore, a seemingly logical goal would be to *maximise knowledge* in order to *minimise risk*. Figure 1-3 created by the researcher attempts to convey the relationship between knowledge and risk, and the corresponding disciplines of knowledge management and risk management, in a simple manner.

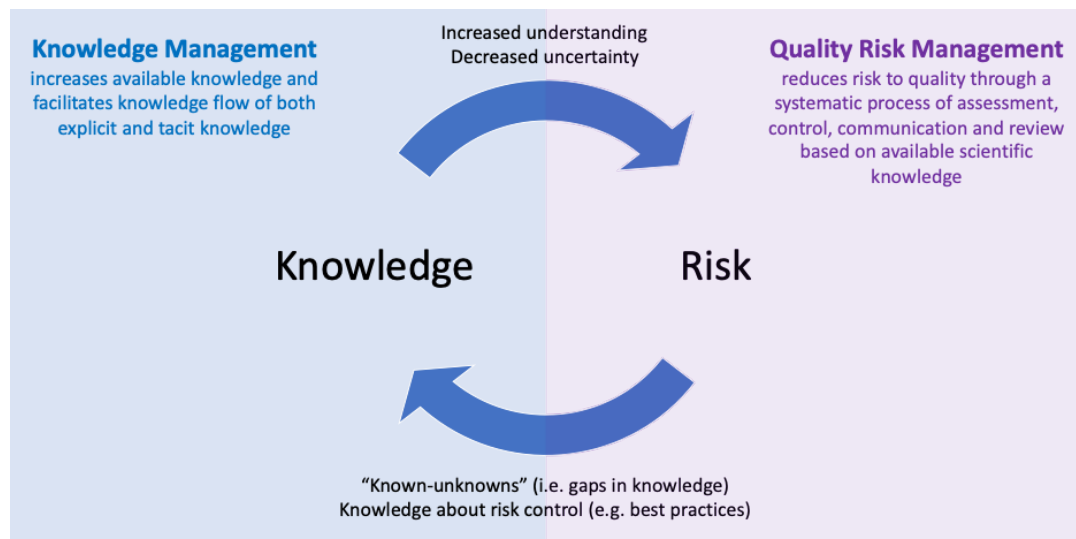


Figure 1-3 – Relating knowledge, knowledge management, risk & risk management

It is acknowledged by the researcher that there are limitations to this ideal state, such as:

- Risk cannot be *completely* eliminated in most situations, even with a high degree of knowledge.
- There are *economic* and other considerations for how much time and expense is invested to maximise knowledge (i.e., at some point, risk will become acceptable even if it could be further reduced).
- There are *scientific limitations* to an organisation’s knowledge and understanding.

Arguably one factor *within* the control of organisations is their ability to effectively apply what is known (i.e., the ‘known-knowns’). This knowledge should be inclusive of knowledge internal and external to the company and should include both explicit⁵ and

⁵ Explicit knowledge refers to documents, pictures, videos, and other codified knowledge.

tacit⁶ knowledge. An organisation applying the best of their knowledge should be a fundamental tenant of how risk management (RM) can leverage knowledge management to maximise understanding and minimise risk.

However, as detailed in Chapter 2 of this thesis (*Literature Review*), there is strong evidence that the pharmaceutical industry's adoption of KM and competency in KM has significantly lagged relative to the adjacent enabler of QRM as shown in the ICH Q10 PQS diagram (Figure 1-2). In fact, KM has been labelled an 'orphan enabler' (Calnan, Greene and Kane, 2018). One must ponder why is it that QRM has progressed in the industry and KM has been left behind?

The most common explanation is that QRM has benefited from having its own regulatory guidance, namely *Quality Risk Management, ICH Q9* (ICH, 2005), while KM has no equivalent. Yet this leaves one wondering *why did that happen?* Why was no guidance provided for KM? While this may itself warrant its own research study, the researcher offers the following insights to address these questions based on his experiences, observations, and review of the literature.

- **Quality risk management is embedded in a PQS based on Good Manufacturing Practices (GMPs), while knowledge management is not.**
QRM and KM are both acknowledged in a PQS based on ICH Q10 and on ISO 9001. But KM is not an identified requirement in a PQS based on GMPs. (ISPE, 2012)
- **Risk management has a head start: risk management has been studied for about 70 years, while knowledge management only for about 30 years.**

⁶ Tacit knowledge refers to knowledge that resides in the minds of individuals and is surfaced in response to a situation or action (APQC, 2019). Common examples of tacit knowledge include decision rationale, knowledge gained through experience, and mental models. Tacit knowledge is often referred to as 'know-how', 'know-why', or 'know-who'.

RM as an area of study is associated with the insurance industry dating back to about 1950 (Dionne, 2013). KM has only been recognised as a discipline since 1991. (Nonaka, 2007).

- **There is an existing body of literature, including many standards, on risk management and related topics.**

One need only look at the references section of ICH Q9 (ICH, 2005) to see there are 17 references, including ten (10) cited ISO and/or IEC standards and three (3) cited books on FMEA, in addition to two (2) other regulatory guidance documents and two (2) other references. Many other standards exist, including from the Project Management Institute (Project Management Institute, 2019), the National Institute of Standards and Technology (NIST, 2016), and elsewhere. Considering KM, given there is no equivalent to ICH Q9, KM is introduced in ICH Q10 (ICH, 2008). There are no references to explain KM, and the definition of KM in ICH Q10 was derived specific to ICH Q10. An ISO standard was not published on KM until 2018 (ISO, 2018) and ISPE industry guidance in 2021 (ISPE, 2021b).

- **Quality risk management is ‘on the radar’ of regulatory authorities and industry groups alike.**

A recent presentation by O’Donnell (O’Donnell, 2020) asked a similar question: Why had QRM progressed relative to KM? In reviewing QRM guidance in the GMPs and other official guidance, O’Donnell identified at least 18 sources of QRM guidance since 2008. When asking the same question of KM, only four instances were noted, and typically these were a single passing reference to KM in the respective document. Similarly, a review of the PDA Technical Report Bookstore (PDA, 2021) includes a series of six Technical Reports focused on QRM, while there are none on KM.

- **Quality risk management is more discrete and better understood than knowledge management.**

QRM implementation in the pharmaceutical industry has been the subject of many studies by academia, industry, and regulators. While there still remain many challenges⁷ with QRM implementation, the core concepts of what QRM is in practice are generally well established. Figure 1 in ICH Q9 (ICH, 2005), included as Figure 1-4 below, conveys the essence of the RM process and several potential tools in the appendix to Q9 support the ‘how.’ Conversely, there is no equivalent figure to convey a generic KM process nor potential tools.

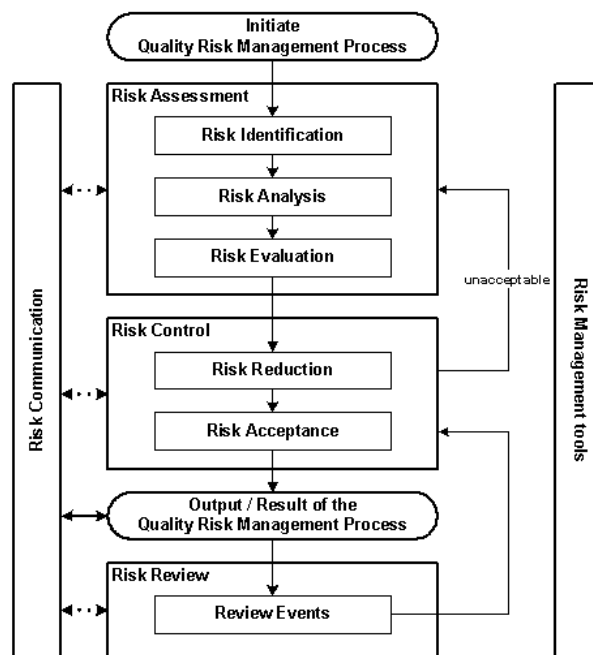


Figure 1-4 – Overview of a typical quality risk management process (Figure 1, ICH Q9) (ICH, 2005)

KM is further complicated as it can overlap with many different disciplines, including Information Technology, Learning & Development, Operational Excellence, Human Resources, and others, thus bringing much diversity of opinion to what KM is and how to do it. A recent survey from Knoco highlights the diversity of organisational alignment for KM functions in companies (Knoco, 2017, 2020). Furthermore, there is a broad diversity of issues for KM to address, which typically require very different approaches to manage both explicit and tacit knowledge. According to Birkinshaw (Birkinshaw, 2001), KM is difficult

⁷ QRM continues to evolve as witnessed by ongoing revision to ICH Q9, continued research and industry focus

because the range of possible approaches and tools to manage knowledge are more highly diverse and subjective and tend to be specific to organisational challenges or business models.

Research presented by Kane in 2018 started to shine a light on this issue of lagging KM adoption in the pharmaceutical industry. Kane emphasised the importance and benefit of managing knowledge as an asset in the pharmaceutical industry, providing a vision for end-to-end product knowledge accessibility and availability, as well as a blueprint for knowledge management (Kane, 2018). The findings and relevance of Kane's research on this study will be explored further in Chapter 2.

Further to lagging KM adoption, another finding of concern to the researcher was the discovery that while QRM and KM are considered highly interdependent, they are not well integrated in practice today. This suggested to the researcher a potential critical gap in the realisation of ICH Q10: that the industry is not ensuring it is applying the best of what it knows to make optimal risk-based decisions. This influenced the direction of the research study, through an effort to develop a mechanism to address this gap. The next sections in this chapter further introduce this research journey.

1.3 Researcher introduction and research positionality

While this research study commenced formally in 2018, in reality it began a decade earlier when the researcher was first introduced to the concept of KM as a member of the MSD⁸ delegation to a US Food and Drug Administration (FDA) *Cooperative Research and Development Agreement* (CRADA⁹) workshop series. This CRADA chartered a cohort of pharmaceutical and biotech companies to explore the industry's adoption of the FDA's new quality initiative for the 21st Century (US FDA, 2002; FDA, 2007; Shanley, 2007). A series of workshops, held in September 2007 and February 2008, explored the

⁸ MSD, or Merck Sharp & Dohme, an American-based pharmaceutical company known as Merck & Co., Inc., Kenilworth, NJ USA in the USA and Canada, and MSD outside of the USA and Canada. Any and all references to 'Merck' throughout this confirmation and associated works are solely in reference to "Merck & Co., Inc., Kenilworth, NJ USA" unless otherwise stated.

⁹ The CRADA is a research agreement between FDA and non-Federal parties to collaborate in developing and moving new technologies to market (FDA, 2018)

practical implementation of the FDA's new quality paradigm which had been formalised through a series of new guidance documents and included preliminary exploration of the concept of *knowledge management*, which was very much in its infancy at the time. This was the researcher's first in-depth exposure to these regulatory guidelines, and more specifically to the role of KM in enabling an effective PQS, which launched a learning journey spanning nearly 15 years. Steps taken and perspectives gained in this journey are explored throughout this thesis. Embarking upon this research study presented the researcher with a unique and exciting opportunity to drive meaningful improvement for the pharmaceutical industry and the patients it serves beyond the organisational boundaries of his employer.

In addition to the CRADA workshop series, the researcher had been a student of KM, business strategy, organisational change management, lean six sigma and related methodologies for over half of his 27+ year professional career. The researcher had been conducting informal research in KM through personal learning, benchmarking, publishing, and speaking as a KM thought leader and subject matter expert within the pharmaceutical industry and across industries since 2008.

A specific example of a significant KM project dating back to 2008 is the researcher initiating a Lean Six Sigma Black Belt certification project to devise a KM strategy for the small molecule commercialisation function at a major multinational pharmaceutical company (MSD). The strategy recommended that a proper KM organisational unit should be created, and the researcher was selected to lead that function. Since then, the KM organisational unit has led a successful KM program for MSD. These activities established a strong foundation for the researcher in theory and practice and have uniquely positioned the researcher for this research study. A timeline summary of key activities in the researcher's KM learning and thought leadership prior to this research study is included in Appendix 1.

Through this professional experience, the researcher has demonstrated a diverse, lengthy, and persistent presence in KM with a variety of global audiences for over a decade. These audiences included regulatory authorities, industry groups, academia,

and organisations outside of the pharmaceutical industry. The researcher has also been active in KM through a variety of channels, including as a speaker, author, panellist, industry SME, guest lecturer at Columbia University and conference planning committee member. These events and more presented opportunities for the researcher to demonstrate thought leadership and influence on a broad scale while at the same time embarking on a rewarding learning journey. These collective experiences inherently formed the researcher's thinking in undertaking this research study.

1.4 Focus of this research study

Initially, the researcher set out to explore two hypotheses focused primarily on improving KM and in particular, KM involving tacit knowledge. These two hypotheses are discussed in detail in Chapter 3 and the essence of which are presented here as follows:

1. The pharmaceutical **sector does not currently have a holistic end-to-end view of what it knows about its products** across the product lifecycle, **nor how to best enable knowledge 'flow'** to ensure the best possible quality- and operational-related outcomes.
2. **Tacit knowledge is critical but is not effectively managed** during key activities across the pharmaceutical product lifecycle, such as technology transfer.

During the course of the study on end-to-end KM, the researcher was struck by the pervasive gap in adoption between QRM and KM as highlighted in section 1.1 of this Chapter. This motivated the researcher to accelerate examination of and reflection on the dual ICH Q10 enablers of QRM and KM in an attempt to challenge the siloed thinking evident in the pharmaceutical industry regarding these topics. This led to a third hypothesis as follows:

3. **Quality risk management and knowledge management are not adequately integrated to ensure the best possible risk-based decisions.** Strengthening the relationship between QRM and KM has the opportunity to improve patient-focused outcomes across the product lifecycle through reduced risk to product quality and availability.

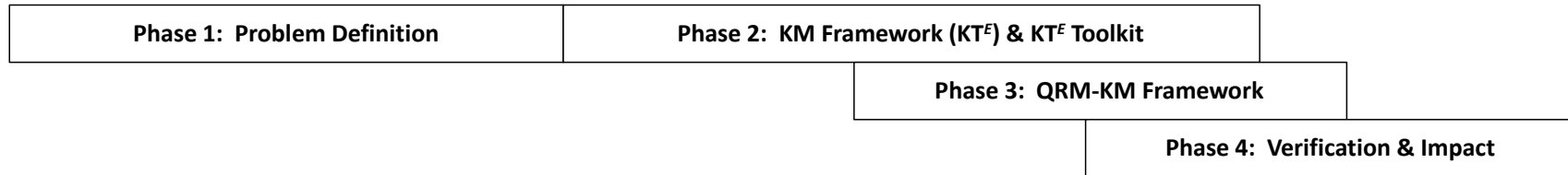
The research study explored each of these three hypotheses; and the journey taken is described in the next chapters of the thesis, beginning with a literature review in Chapter 2. Notably, the research activities for this study were in parallel and iterative, and not necessarily in the order presented. While setting the context, the researcher believed it to be useful to introduce some of the primary outputs of the study at this stage.

1.5 Overall timeline and progression of the research

As noted previously, the research as described in the thesis was iterative in nature and while the study initially embarked with a focus on improving knowledge management for technology transfer (hypotheses 1 and 2), the emergence of the importance of the QRM-KM interdependency (hypothesis 3) changed the course of the research. This is reflected by the order in which this research is presented in this thesis. However, it is useful to introduce an overall timeline and progression of the research. This timeline, consisting of four phases, is shown in Figure 1-5. The numbered activities highlight many of the outward-facing research activities (e.g., conference presentations, papers published) and four primary outputs which are discussed in the next section.

Complete details of the key research activities as depicted in Figure 1-5 are provided in Appendix 2.

Research Phases



Key Research Activities

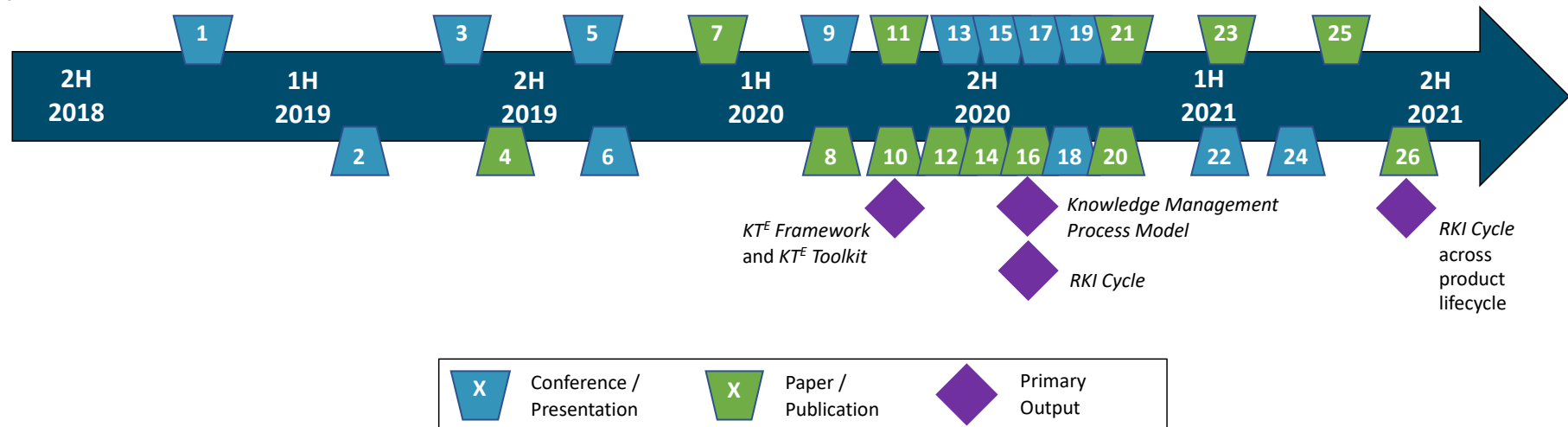


Figure 1-5 – Timeline of research activities

1.6 Primary outputs of this study as relevant to the PQS

This research study resulted in many outputs, outcomes, and impacts as discussed in detail in Chapter 10. Several of these outputs are expected in time to have a potentially significant impact on at least four areas of the PQS. These four areas of the PQS are identified in Figure 1-6.

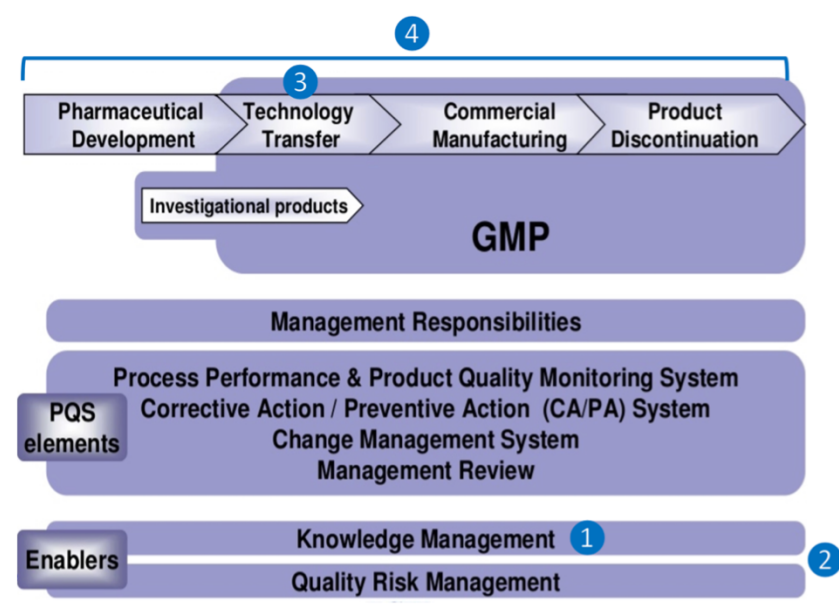


Figure 1-6 – Anticipated impact of this study on the PQS

The following primary outputs which impact each of these PQS areas are as follows (the output is noted in **bold** and the PQS area is underlined, and maps to Figure 1-6):

1. Development of a **Knowledge Management Process Model** to define a process for KM as an enabler of the PQS.
2. Development of the **Risk-Knowledge Infinity Cycle (RKI Cycle)** framework to define the relationship between QRM and KM as the dual enablers to the PQS.
3. Development of a **Knowledge Transfer Enhancement Framework (KTE^E Framework)** to define a plan and toolkit for KM during the PQS lifecycle stage of technology transfer.
4. Demonstration of *RKI Cycle* application and impact **across the pharmaceutical product lifecycle** to illustrate the PQS dependency on effective KM and to rapidly scale these new frameworks across the product lifecycle by maximising knowledge to minimise risk.

The following is an introductory explanation of each of these outputs.

1.6.1 Knowledge Management Process Model

A *Knowledge Management Process Model* (Figure 1-7), was strategically crafted similar to the familiar (and perhaps iconic) QRM Process Model found in ICH Q9 (ICH, 2005). The researcher believes that this model has the potential to enhance the understanding of knowledge management as an equal party to QRM in enabling an effective PQS. This model is fully introduced and discussed in Chapter 4 of this thesis.

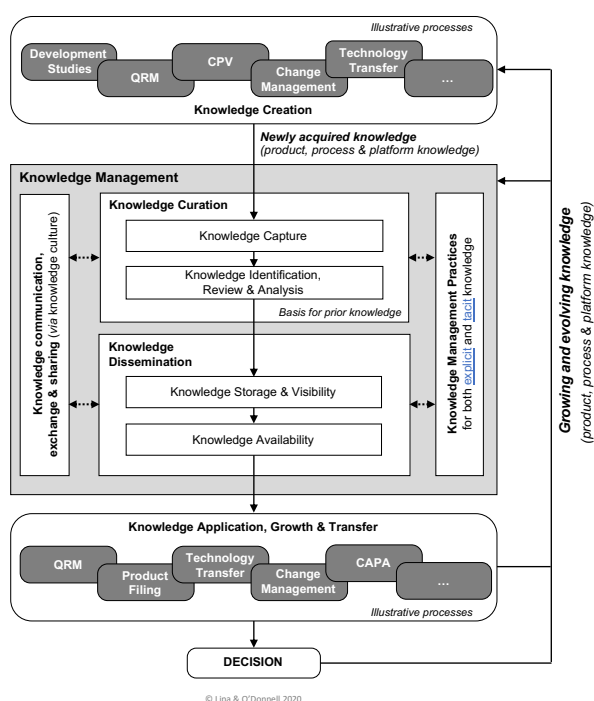


Figure 1-7 – KM Process Model (preview)

1.6.2 Risk-Knowledge Infinity Cycle Framework

The development of the *Risk-Knowledge Infinity Cycle (RKI Cycle)* Framework (Figure 1-8) may well be the most exciting output of this research study. Based on its broad appeal and the interest since its publication in October 2020 (Lipa, O'Donnell and Greene, 2020a) and a subsequent survey assessing the utility of the *RKI Cycle*, the framework is already attracting significant attention, even before this thesis was written. This framework is fully introduced and discussed in Chapter 5 of this thesis.

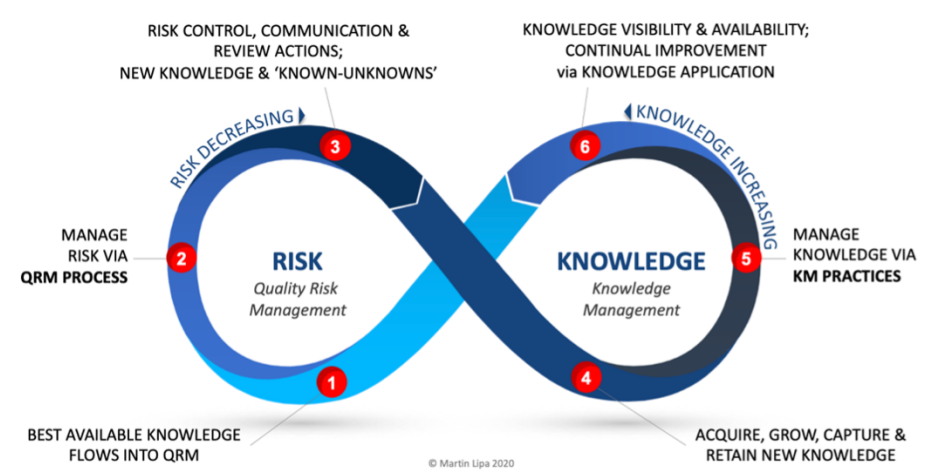


Figure 1-8 – The Risk-Knowledge Infinity Cycle (as applied to ICH Q10, preview)

1.6.3 Knowledge Transfer Enhancement (KT^E) Framework

The development of a framework for *Knowledge Transfer Enhancement (KT^E Framework)* offers a pragmatic ‘how’ to guide KM and knowledge transfer (KT) during the critical lifecycle stage of technology transfer. In addition, an accompanying *KT^E Toolkit* is proposed, along with case studies and demonstrated impact of tacit knowledge transfer approaches. This framework and toolkit are fully introduced and discussed in Chapter 7 of this thesis.

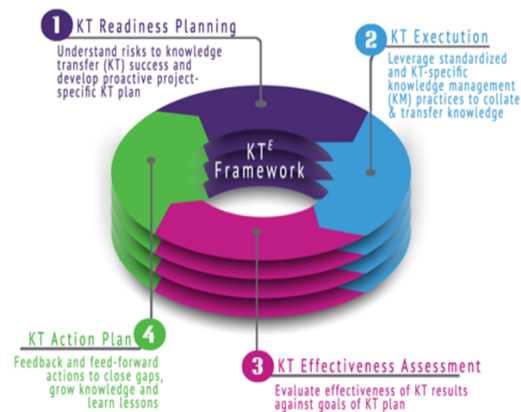


Figure 1-9 – KT^E Framework (preview)

1.6.4 Demonstrating how the RKI Cycle can be applied across the product lifecycle

Finally, building on all of these outputs, a mapping of KM focus and associated KM methods and tools was carried to demonstrate how the *RKI Cycle* can be applied across the end-to-end product lifecycle. This mapping, along with two additional examples

which illustrate application of the *RKI Cycle* to change management during commercial manufacturing and to data analytics, illustrates the potential broad impact of the *RKI Cycle*. These examples illustrating the *RKI Cycle* across the product lifecycle are fully introduced and discussed in Chapter 8 of this thesis.

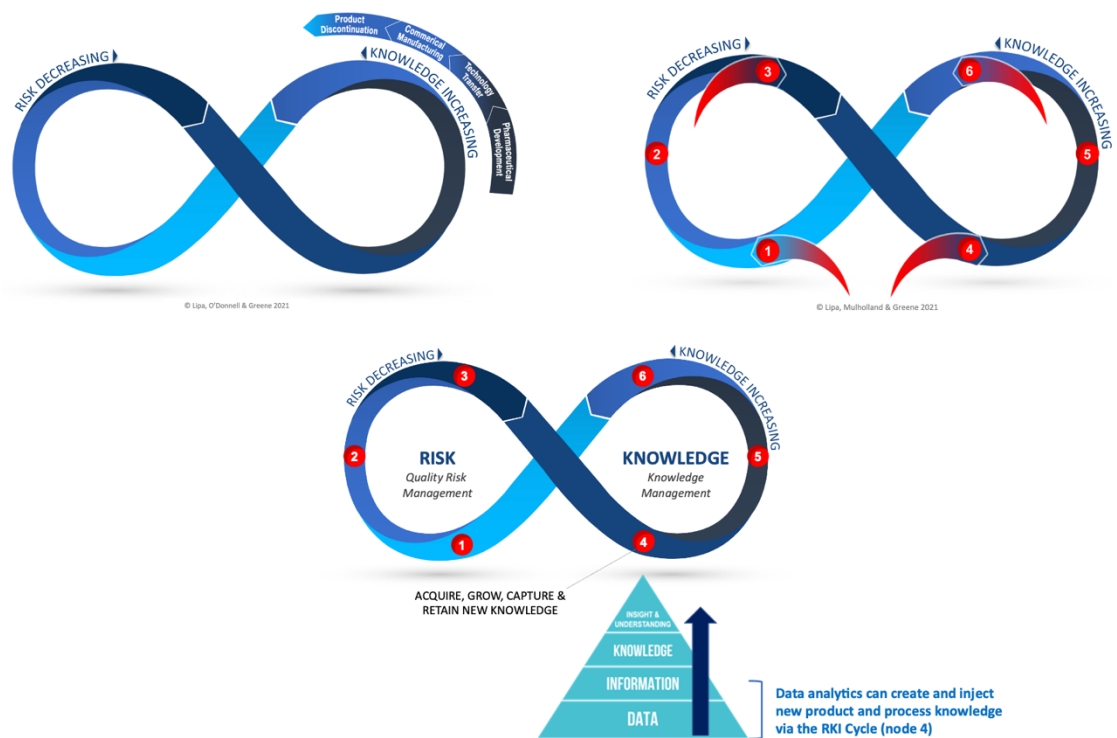


Figure 1-10 – The RKI Cycle applied across the product lifecycle – examples (preview)

In addition to each of these models and frameworks, the research study has fostered a dialogue of learning and education in the exchange of ideas and socialisation of concepts, touching several hundreds of people during the course of this study. Furthermore, it is in the translation of theory to practice through these models, frameworks, and maps that the researcher finds the greatest motivation and energy, with the ambition of influencing a large industry and ultimately having a tangible impact on the lives of patients served by this important industry.

This chapter has introduced the research study background and context. The next chapter provides a review of the main literature sources considered as part of this research study.

Chapter 2: Literature Review

The purpose of this chapter is to provide a summary of the relevant literature considered for this research study. The literature review focused on a variety of topics, including the primary topics of knowledge management, risk management and technology transfer, and did so both within and beyond the pharmaceutical sector. Importantly, the literature review also examined a variety of *intersections* between topics to better discern relationships and adjacencies. Figure 2-1 was designed to convey the scope of the literature review and also how the various topics relate. The three large circles represent the main areas of focus, while the smaller (purple) circles represent related topics reviewed. Figure 2-1 also provides a mapping of where the various topics are covered in this thesis.



Figure 2-1 – Scope of literature review

The review of each topic within this chapter will typically follow a progression from more general (e.g., managing knowledge across the product lifecycle) to more specific (e.g., managing knowledge specifically for technology transfer as a stage in the product lifecycle). Where applicable, for a given topic this review will first address regulatory

guidance, followed by industry guidance, and finally other academic or research-related literature.

It is useful to provide a brief explanation of pharmaceutical sector context as there a variety of different organisations cited during the course of this study, with different and sometimes overlapping missions. This research study will reference a sector comprised of three primary cohorts: *industry* (for-profit organisations which provide a pharmaceutical product or associated service); *regulatory agencies* (authorities which have legal authority to regulate the pharmaceutical industry in their respective countries); and *academia*. In addition, there are a variety of associations which comprise of a mix of these cohorts.

- Most notably referenced in this study *ICH*, the International Council for Harmonisation. For the context of this study, ICH has authored a variety of guidelines which are widely adopted by worldwide regulatory authorities. Successful implementation of ICH guidelines forms a core focus of this research study, given their importance, relevance, and global reach.
- Also of significance to this study are the professional associations of *ISPE* (International Society for Pharmaceutical Engineering) and *PDA* (Parenteral Drug Association), which each provide a venue for cross-stakeholder dialogue and exchange of ideas to advance the industry. One feature of these associations is the creation of ‘best practices’, authored by industry subject matter experts, to support the industry in technical and regulatory success.
- Another industry association referenced within this research study is *BioPhorum*, although this association is primarily comprised of industry and focused on connecting leaders and experts across industry members to share best practices and align on industry positions.

These stakeholders and associations will be referenced regularly through this research study. The following diagram (Figure 2-2) is intended to help the reader understand these various entities and serve as a helpful ‘quick reference guide’ throughout this document.

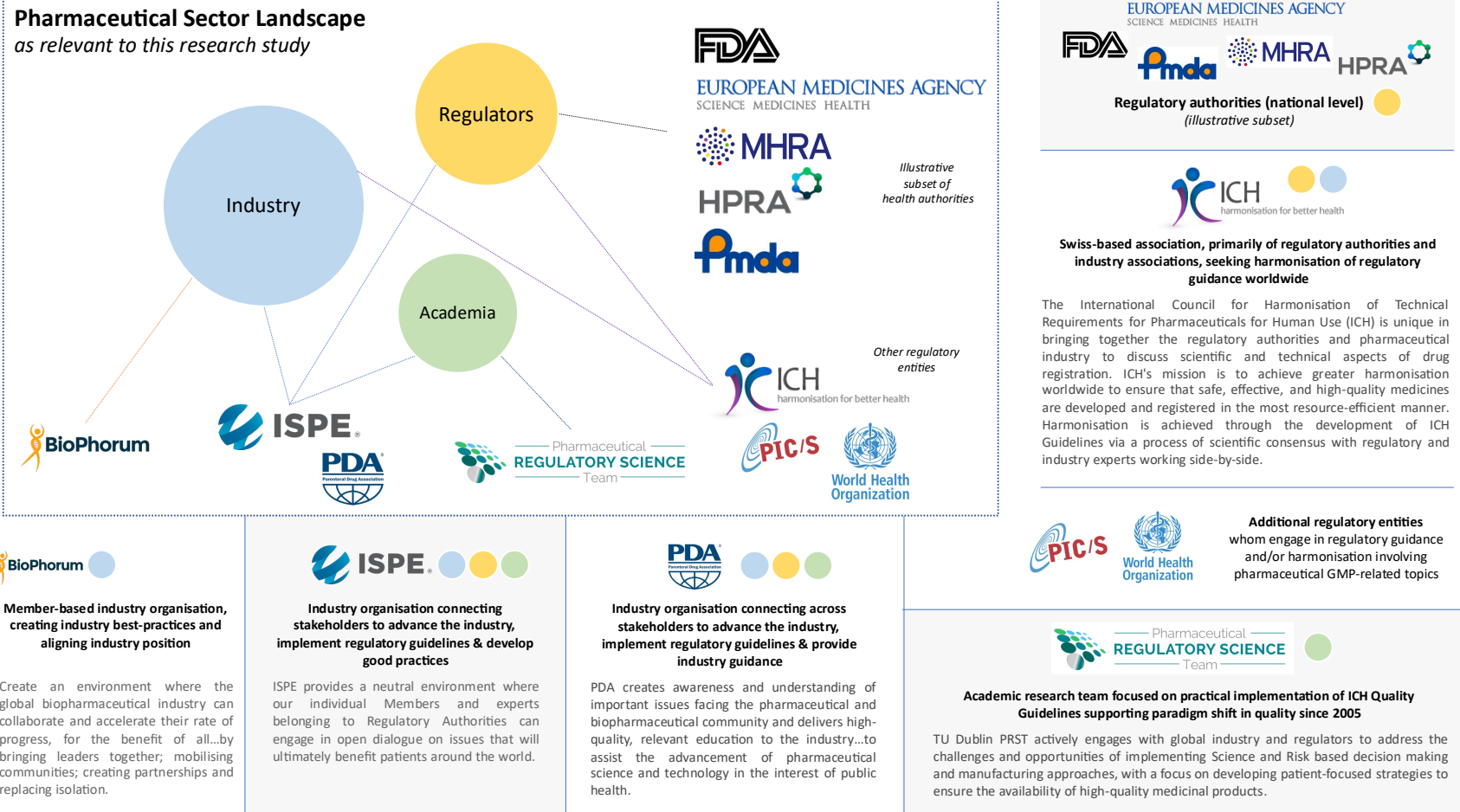


Figure 2-2 – Pharmaceutical Sector Landscape¹⁰

¹⁰ Descriptions for BioPhorum, ISPE, PDA, PRST and ICH are taken from their respective *About* pages (BioPhorum, 2020; ICH, 2020; ISPE, 2020; PDA, 2020; PRST, 2020).

2.1 Managing knowledge across the product lifecycle

Several definitions of knowledge management are presented in Table 2-1 to formally define the concept. In the opinion of the researcher, the diversity seen across these definitions is the first clue of the variability and lack of common understanding of what KM is.

Table 2-1 – Definitions of Knowledge Management

Source	Knowledge Management Definition
Cambridge Business Dictionary (Cambridge, 2021)	The way in which knowledge is organised and used within a company, or the study of how to effectively organise and use it.
ICH Q10 (ICH, 2008)	Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components
ISO Standard 30401 (ISO, 2018)	Management with regard to knowledge. note 1: It uses a systemic and holistic approach to improve results and learning. note 2: It includes optimising the identification, creation, analysis, representation, distribution, and application of knowledge to create organisational value.)
APQC ¹¹ (APQC, 2018)	Systematic approaches to enable knowledge and information to grow, flow and create value; connecting people to people and people to content.

2.1.1 Regulatory guidance

This section includes a review of *Regulatory Guidance* literature and includes discussion specifically related to explicitly stated *knowledge management* expectations as well as references to expectations for *managing knowledge* during the product lifecycle. The scope of literature surveyed represented diverse sources of guidance which are common inputs to shape an organisation's PQS as follows:

- International Conference on Harmonisation (ICH) Quality Guidelines, including
 - ICH Q8(R2): Pharmaceutical Development (ICH, 2009)
 - ICH Q9: Quality Risk Management (ICH, 2005)
 - ICH Q10: Pharmaceutical Quality System (ICH, 2008)
 - ICH Q8/Q9/Q10 Questions & Answers (ICH, 2010)
 - ICH Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) (ICH, 2012)

¹¹ APQC, or American Productivity & Quality Center, is a global authority in KM. www.apqc.org.

- ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (ICH, 2019)
- World Health Organisation (WHO) Guidelines, including:
 - WHO Good Manufacturing Practices for Pharmaceutical Products: Main Principles (WHO, 2014)
- EudraLex Volume 4 – Good Manufacturing Practice (GMP) Guidelines (Part I) (European Commission, 2012)
- Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medical Products (Part 1, Chapter 1) (PIC/S, 2018)

Perhaps of note, no specific US FDA guidance is listed above. FDA has participated in the development of ICH Quality Guidelines listed above and has subsequently adopted these guidelines. Therefore, FDA guidance is included through the ICH documents.

2.1.1.1 ICH Quality Guidelines

Examining the ICH Quality guidelines sequentially starting with **ICH Q8**, *Pharmaceutical Development* (ICH, 2009), ICH Q8 establishes a risk-based approach to product development commonly referred to as *Quality by Design* (QbD). While there is only a singular reference to KM in ICH Q8 (which directly references ICH Q10 (ICH, 2008)), ICH Q8 aptly sets the stage for the expectations of applying knowledge to increase product and process knowledge and make scientific- and risk-based decisions. Furthermore, ICH Q8 acknowledges that new knowledge will be gained over the product lifecycle, for example as follows (note the specific acknowledgement for knowledge gained from ‘failed’ experiments):

Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful (ICH, 2009).

ICH Q8 also introduces the concept of *prior knowledge*. This concept is not directly defined – its meaning can only be inferred as appropriately vetted and managed knowledge already existing in the organisation or other reputable source (e.g., from

prior products, scientific literature), and industry has continued to debate this at conferences (CASSS, 2018).

ICH Q9, *Quality Risk Management* (ICH, 2005) 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.’ QRM is identified in ICH Q10 as an enabler adjacent to KM (ICH, 2008) yet there is no acknowledgement of KM as a dual enabler, nor corresponding guidance for KM.

A comprehensive literature review of pharmaceutical regulatory guidance as it pertains to KM was conducted recently by Kane (Kane, 2018), which covered in particular detail **ICH Q10, *Pharmaceutical Quality System*** (ICH, 2008) and its approval. This included a review of the positioning of KM as an enabler to the PQS, the definition of KM prescribed by ICH Q10 and the KM-specific questions and answers in the supplemental Q8/Q9/Q10 Questions & Answers document (ICH, 2010). Therefore, the researcher will not repeat this review but will summarise relevant key points.

1. The term *knowledge management* is defined in ICH Q10 as ‘[a] systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components.’ While a valid definition, in the opinion of the researcher and as evidenced by subsequent literature invoking the need for ‘know-how’ and other forms of tacit knowledge (ISPE, 2018), this definition is arguably narrow and focused primarily on explicit knowledge (i.e., documented knowledge).
2. The scope of KM spans the entire product lifecycle as is identified in ICH Q10 section 1.6.1, ‘Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation.’ In addition, section 1.6.1 provides examples of sources of knowledge, which include but are not limited to ‘prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities.’ As one might discern, these are very broad

buckets of knowledge collectively covering many different processes (e.g., development studies) and activities (e.g., innovation) across the lifecycle.

3. The supplemental Q8/Q9/Q10 Q&As (R4) document (ICH, 2010) provides useful clarification to a variety of questions across this trio of guidelines, including for KM within ICH Q10. Key themes from these answers include that there is no prescribed 'how' to implement KM, that there are no specific dedicated computerised information management system requirements and there are no regulatory requirements for a formal KM system, although 'it is expected that knowledge from different processes and systems will be appropriately utilised.'

The key representation of the pharmaceutical product lifecycle, the PQS and its two enablers from ICH Q10 shown in Figure 1-2 is of foundational importance and is referenced throughout this thesis.

The importance of managing knowledge through acquisition, application and sharing is further reinforced in **ICH Q11, Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)** (ICH, 2012) as it introduces the concept of proactive knowledge transfer across an organisation, specifically:

Knowledge gained from commercial manufacturing can be used to further improve process understanding and process performance and to adjust the control strategy to ensure drug substance quality...the knowledge and process understanding should be shared as needed to perform the manufacturing process and implement the control strategy across sites involved in manufacturing the drug substance.

ICH Q11 further reinforces the expectation for a 'systematic approach to managing knowledge related to both drug substance and its manufacturing process through the [product] lifecycle', inclusive of technology transfer activities.

The final version of **ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management**, (ICH, 2019) adopted in late 2019, positions KM in a central role with respect to the change management process relating

to post-approval changes. ICH Q12 builds upon the KM foundation established by ICH Q10 in order to ensure the latest, most comprehensive, and most accurate knowledge is applied to maintain the state of control and enable continual improvement. Furthermore, an effective KM capability acting as a PQS enabler, helps to ensure that knowledge is available to support other critical activities including RM and CAPA as well as post-approval changes. A representation of the positioning of knowledge and knowledge management in conjunction with change management in ICH Q12 is depicted in Figure 2-3.

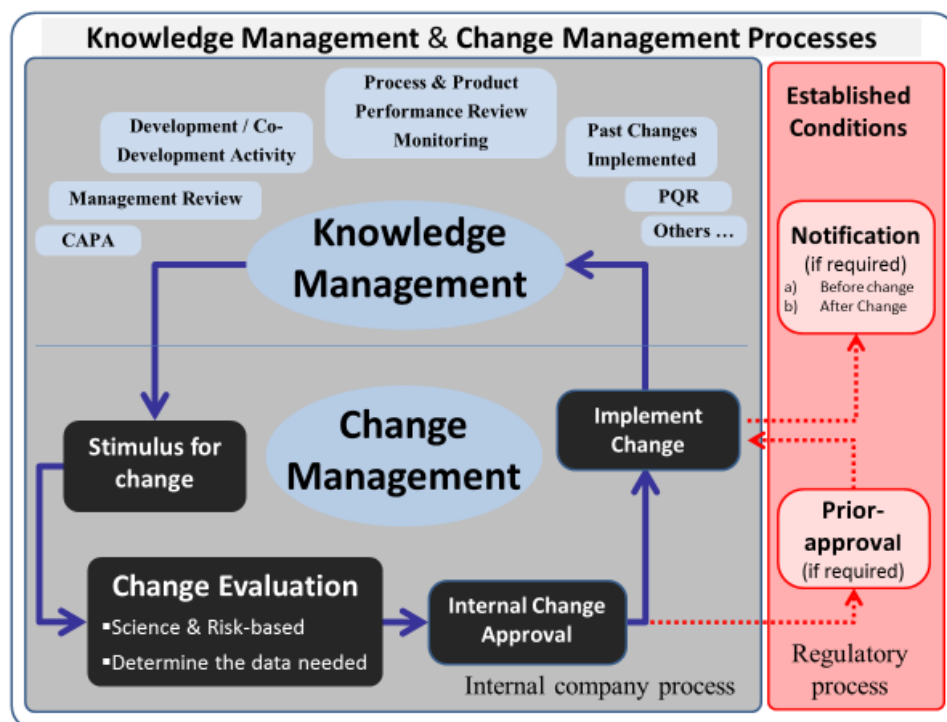


Figure 2-3 – Knowledge management and change management processes (ICH, 2019)

This interaction is further explained in appendix 2 of ICH Q12 as follows (emphasis in bold added by the researcher):

*An effective change management system includes **active knowledge management**, in which **information from multiple sources is integrated** to identify stimuli for changes needed to improve product and/or process robustness. The connection between knowledge management and change management is illustrated in [Figure 2-3]. These sources can include, but are not limited to, developmental studies, process understanding documents, product or process trending, and product-specific CAPA outcomes. **Provisions should be***

*made for sharing knowledge (e.g., in quality agreements and/or contracts) that relates to product and process robustness or otherwise informs changes between the MAH and relevant manufacturing stakeholders (research and development organisations, manufacturers, CMOs, suppliers, etc.)... As described in ICH Quality Implementation Working Group on Q8, Q9, and Q10 Questions & Answers, there is **no added regulatory requirement** for a formal knowledge management system.*

Key concepts which may be extracted from this guidance include that:

- Knowledge management is an intentional and proactive activity, covering a diverse set of process and product knowledge.
- Knowledge management is also invoked as a means to sharing knowledge across a diverse set of stakeholders.

2.1.1.2 WHO Guidelines GMP for Pharmaceutical Products: Main Principles – Annex 2

The current version of the WHO Good Manufacturing Practices for Pharmaceutical Products: Main Principles (WHO, 2014) includes an expectation for managing product knowledge across the lifecycle as follows:

The PQS appropriate to the manufacture of pharmaceutical products should ensure that...product and process knowledge are managed throughout all lifecycle stages.

The responsibility for KM is identified as an expectation to be defined in establishing a contract with a separate manufacturing organisation but the term is not expressly defined.

2.1.1.3 EudraLex Volume 4 – Good Manufacturing Practice (GMP) Guidelines (Part I)

In EudraLex Volume 4 (Good Manufacturing Practice guidelines), Chapter 1 (Pharmaceutical Quality System) (European Commission, 2012), the following expectations are established (emphasis in bold added by the researcher):

*A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that...**Product and process knowledge is managed throughout all lifecycle stages***

and

Continual improvement is facilitated through the implementation of

quality improvements appropriate to the current level of process and product knowledge.

2.1.1.4 PIC/S Guide to Good Manufacturing Practice for Medical Products

No specific expectations of KM across the lifecycle are noted within PIC/S Guide to Good Manufacturing Practice for Medical Products (Part 1, Chapter 1) (PIC/S, 2018), with the exception of a reference to contractual agreements where the responsibility for KM should be appropriately noted. However, the expectations for managing knowledge are noted as part of a firm's PQS similar to that of EudraLex Volume 4 Part 1 (European Commission, 2012) (emphasis in bold added by the researcher):

*A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that...**Product and process knowledge is managed throughout all lifecycle stages...[and] continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge.***

2.1.2 Industry guidance

This section includes a review of pharmaceutical *Industry Guidance*¹² literature from industry associations and other authorities. This review focused on the expectations for KM across the product lifecycle. As discussed previously in this thesis, there is a general lack of pharmaceutical industry guidance for KM. However, recently there have been some developments within the industry towards addressing this gap.

2.1.2.1 ISO

In November 2018 the International Organisation for Standardisation published its first ever guidance on KM in the form of *International Standard ISO 30401:2018(E), Knowledge Management Systems – Requirements* (ISO, 2018). This standard acknowledges in the introduction that KM has no single accepted definition, and no global standards predate the subject standard. The standard also stated there are many

¹² The concept of *industry guidance* literature in the pharmaceutical industry is important as these are typically documents authored by cross-functional SME teams and undergo a peer-review commenting process for broad sector input. Input to these guides is often sought from industry, academia, and regulatory authorities. These guidance documents typically help industry understand how to satisfy regulations, adopt good practices, etc.

well-known barriers to KM and confusion with other disciplines. In addition, the standard describes the importance of KM in a generalised manner to an organisation's success.

The standard does not deeply address specific KM approaches, nor does it use the word 'tacit' (however it does state that at one-point knowledge includes 'insights and know-how' as common vernacular for tacit knowledge). The standard is useful in particular for organisations looking to set up or improve their KM programs. It addresses a lifecycle of knowledge activities and inventories KM enablers, including culture. It covers the expectations of leadership, policy, roles and responsibilities, and support requirements (e.g., communications). The standard has not seen rapid uptake, with nearly half of survey respondents in the Knoco¹³ 2020 KM survey (Knoco, 2020) unaware of the standard or not intending to buy or use it, and only a very small percentage (2%) are seeking or have achieved certification. In the opinion of the researcher, this should change over time as more become familiar with its contents and the importance of KM.

2.1.2.2 ISPE

In 2019 ISPE chartered a team to create a *Good Practice Guide for Knowledge Management*, and the researcher was invited to be a member of the subject matter expert authoring team. ISPE Good Practice Guides are premier industry guidance documents which are authored by industry subject matter experts, and through a governance process are peer reviewed by industry. The following is an excerpt from the ISPE Knowledge Management Good Practice Guide charter¹⁴.

Knowledge Management – one of the two identified enablers of ICH Q10. The publication of ICH Q10 in 2008 saw the formal designation of Knowledge Management (KM) as a key enabler for an effective Pharmaceutical Quality System. Since then, the industry has acknowledged the importance of managing knowledge across the lifecycle to enhance process understanding, improve

¹³ Knoco was established in 1999 by key members of BP's (British Petroleum) global KM Consulting team, who had been recognised in the 1990s as pioneers in the field of KM. www.knoco.com.

¹⁴ The charter is not published, but the charter was available to the researcher as a member of the SME author team for the guide.

decision making and enable more robust risk management. ICH Q10 and the forthcoming Q12 discuss the expectations for firms to proactively manage product and process knowledge citing the potential of more efficient and effective regulatory oversight (e.g., ICH Q12). There are currently few resources, and NO INDUSTRY GUIDANCE available which address the role of Knowledge Management specifically for the pharmaceutical industry.

The chartering of an ISPE Good Practice Guide team for Knowledge Management is an important recognition of the significance of KM and the need for industry guidance. This ISPE Guide was published nearly concurrently with this thesis in May 2021 (ISPE, 2021b) and will be discussed in further detail in Chapter 10.

2.1.2.3 BioPhorum

In March 2020 BioPhorum published a peer-reviewed case study titled *Knowledge Mapping for the Biopharmaceutical Industry: A Test Case in CMC¹⁵ Business Processes from Late-Stage Development to Commercial Manufacturing* (BioPhorum Operations Group, 2020). The purpose of the document was to demonstrate a ‘best practice KM methodology to capture a process-based knowledge map for a major business process’ – in this case for the CMC business process from late-stage development to commercial manufacturing. The intent was to illustrate the knowledge mapping method, produce a company agnostic knowledge map as a reference for the industry, to highlight the common issues with ‘knowledge flows’ where improvements can be made, and to highlight the detailed tacit knowledge which exists in the business process. This knowledge map was created by 18 individuals from 12 different organisations, as listed in the referenced document (BioPhorum Operations Group, 2020). The researcher was an invited member of the team and was responsible for providing the knowledge mapping process and trained the team on knowledge mapping. While not official guidance, this guide will serve a model of knowledge mapping for others to follow as well as having created a useful industry asset in the form of the subject knowledge map.

¹⁵ Chemistry, Manufacturing and Controls (CMC) of a medicinal product is the body of information that defines not only the manufacturing process itself but also the quality control release testing, specifications and stability of the product (Genpact, 2021)

2.1.3 The Pharmaceutical Regulatory Science Team

The Pharmaceutical Regulatory Science Team (PRST) based in TU Dublin has continued to progress research on quality risk management, knowledge management and related topics covered by ICH Quality Guidelines, most recently ICH Q12 (ICH, 2019). The PRST was founded in 2005 in response to the drive for a paradigm shift in quality from the international regulatory community. PRST actively engages with global industry and regulators to address the challenges and opportunities of implementing Science and Risk based decision making and manufacturing approaches. PRST research emphasis is on the development of patient-focused strategies to enable those involved in the manufacture of drug products to meet the evolving international regulatory expectations ensuring the availability of high-quality medicinal products.

An overview of the research topics, currently active researchers (with primary topic) and key regulatory and industry developments is depicted in Figure 2-4. One of the powerful characteristics of the PRST research structure is that research is not done in 'silos' – there is a high degree of research cross-over between these important PQS topics which brings diverse viewpoints and further strengthens the validity of the research overall. The PRST are all active members of industry conferences and publish regularly.

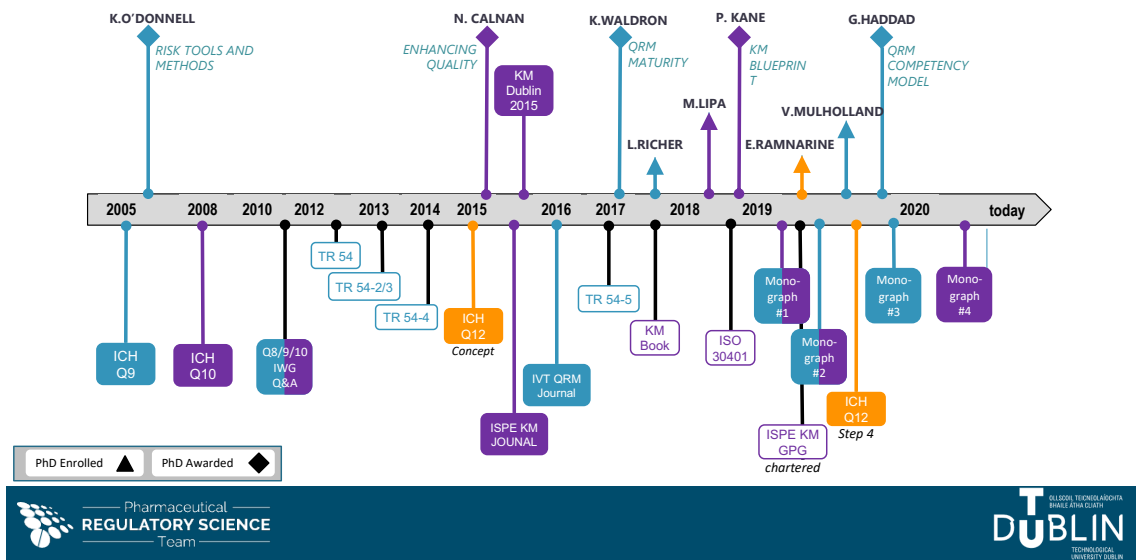


Figure 2-4 – PRST journey in regulatory science research

2.1.3.1 Research by the PRST: Knowledge management

This most relevant research for this research study is the work of Calnan and Kane. Calnan’s 2015 thesis, *Protecting the Patient: Enhancing the Quality of Pharmaceutical Products* (Calnan, 2014a) explored the unacceptable risks that patients are exposed to due to challenges which exist in the complex pharmaceutical product lifecycle.

Calnan’s exploration of KM as an ‘*orphan enabler*’ to the PQS established the foundations for the PRST in KM. Calnan discussed the concepts of tacit and explicit knowledge, the concept of knowledge flow and the link between the importance of capturing and applying knowledge to an effective PQS. Calnan also proposed that the elements of the PQS (product performance and product quality monitoring system, CAPA, change management and management review) should operate through well-integrated and balanced enablers of KM and QRM.

Calnan explored the topics of *being excellent* and *cultural excellence*, in addition to the aforementioned *knowledge excellence* focus. A key output from the research was a construct of the *Building Blocks of Cultural DNA of Quality* (Figure 2-5), in which these

elements of *knowledge excellence, cultural excellence, patient focus* and *being excellent* converge to create a culture of quality.



Figure 2-5 – Building blocks of the cultural DNA of quality (Calnan, 2014a)

The primary research output of Calnan’s work was the *Excellence Framework* (Figure 2-6), a combination of the cultural excellence of a learning organisation with excellence in knowledge creation and utilisation, in order to deliver operational excellence based on a relentless restlessness for improvement. The model is dynamic and encourages one to analyse the current situation for improvement opportunities, to assimilate the findings to create new knowledge and then use this knowledge to take action, decisions and deliver solutions. Reflection is promoted to confirm the effectiveness of the action taken and share lessons learned.

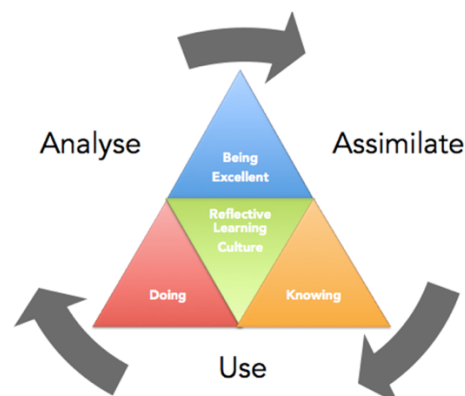


Figure 2-6 – The Excellence Framework (Calnan, 2014a)

Calnan’s work also produced additional KM-related outputs, including a KM e-journal published by ISPE, an informative history of product quality, and a detailed literature

review, including that of knowledge management, found in Chapter 2 of Calnan's thesis (Calnan, 2014a).

The second closely related research study was carried out by Kane, culminating with the 2018 thesis on *A Blueprint for Knowledge Management in the Biopharmaceutical Sector* (Kane, 2018). Kane's focus was on exploring the level of adoption and capability of KM in the biopharmaceutical sector. In finding a general lack of maturity in the sector, Kane's research produced a collection of assets for the sector to leverage to unlock their knowledge. The primary output of the research was a new framework entitled the Pharma KM Blueprint (Figure 2-7).

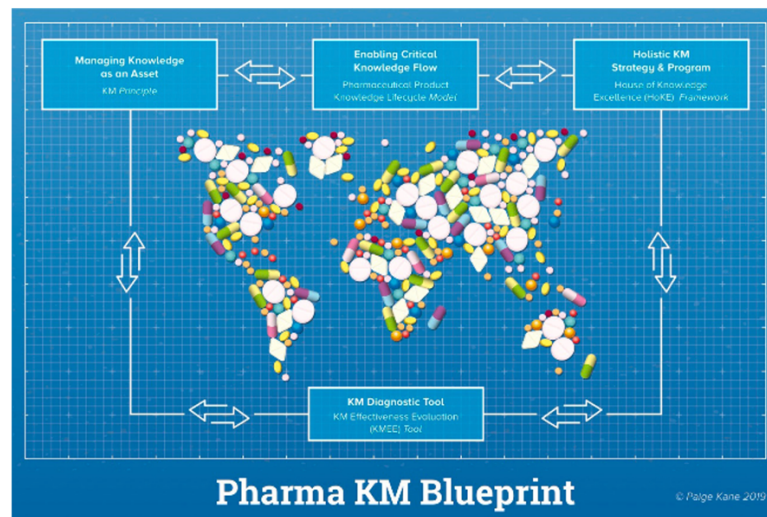


Figure 2-7 – The Pharma KM Blueprint (Kane, 2018)

This framework provided a construct of principles, models and tools summarised as follows:

1. **Managing Knowledge as an Asset** – addresses the need to value and maintain knowledge assets in the same way as physical assets within an organisation.
2. **The Pharmaceutical Product Knowledge Lifecycle Model (PPKL)** (Figure 2-8) addresses the challenge of enabling knowledge flow in order to increase visibility, to access and use the product and process knowledge assets across the product lifecycle.
3. **The House of Knowledge Excellence Framework** (Figure 2-9) demonstrates a framework developed to implement a systematic KM programme linked to strategic objectives of an organisation, incorporating KM practices, pillars

(people, process, technology, governance), and enablers to support the effective management and flow of knowledge assets.

4. **Knowledge Management Effectiveness Evaluation** provides a practical KM diagnostic tool that may be used to identify and evaluate areas of opportunity and to track progress on closing knowledge gaps.

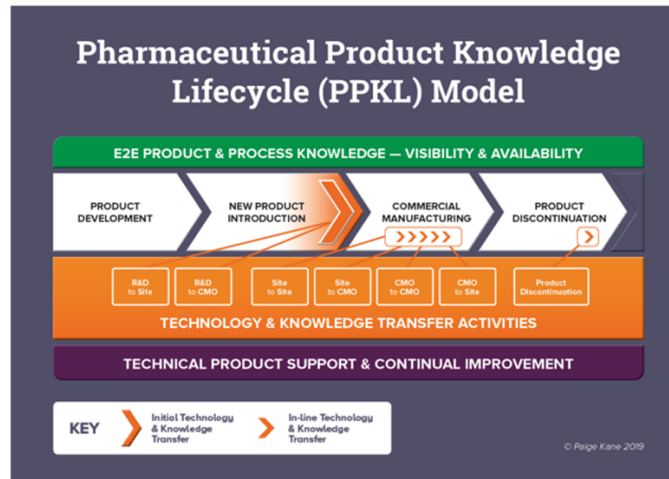


Figure 2-8 – Pharmaceutical Product Knowledge Lifecycle Model (PPKL) (Kane, 2018)

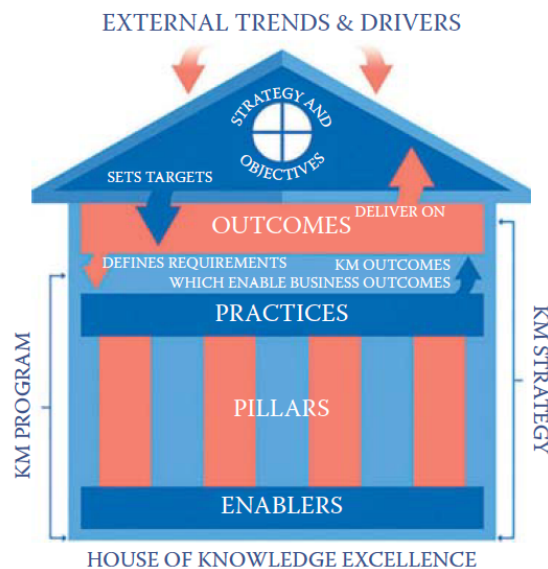


Figure 2-9 – The House of Knowledge Excellence (Kane, 2018)

Of primary relevance to this thesis is the PPKL model. The features of the model include:

- The vision for end-to-end (E2E) product and process knowledge asset visibility, transparency, and availability in order to enable knowledge flow of critical knowledge to those that need it throughout the product lifecycle.
- The addition of a new lifecycle phase of New Product Introduction (NPI) to replace the Technology Transfer lifecycle phase.
- That Technology Transfer is an activity that may occur multiple times across the product lifecycle.
- The addition of a new E2E process to capture the Technical Product Support and Continual Improvement activities that occur across the product lifecycle.

This model provides a helpful anchor to the management of product knowledge and the focus on technology transfer as a focal part of this thesis, in particular to the concepts that knowledge must be managed end-to-end throughout the product lifecycle, that technology transfer is a repetitive activity across the product lifecycle, and capturing the end-to-end knowledge can aid in continual improvement.

The *House of Knowledge Excellence* framework is relevant in particular to the chapter in this thesis which proposes a toolkit for knowledge management during technology transfer (Chapter 7). The researcher co-developed this framework with Kane and was co-author of the book chapter in which it is described (Kane and Lipa, 2018).

Kane's work also produced a thorough literature review on KM, found in Chapter 2 of Kane's thesis (Kane, 2018). As such, the literature review conducted in this thesis did not repeat all of these specifics and instead builds on this literature review (and that of Calnan), with a focus on aspects of relevance to the planned research for this study and developments since Kane's research concluded. Together, the combined literature review across these three theses captures a rich and comprehensive review of the KM literature, especially relative to the biopharmaceutical industry.

These assets will be further referenced throughout this thesis where appropriate. Kane's work is further summarised in a monograph entitled *Advancing Knowledge Management (KM) as an ICH Q10 Enabler in the Biopharmaceutical Industry* (Kane and Lipa, 2020).

In addition, the results of a survey entitled *Knowledge Management Implementation, A Survey of the Biopharmaceutical Industry* were published in May 2020 by ISPE (Kane *et al.*, 2020). This survey was a follow on from Kane’s research and reported on current state of KM implementation, including status of KM implementation, areas of KM focus, primary KM approaches, cultural issues. This survey report further confirmed the relatively low maturity and high variability in which KM is being pursued in the industry.

2.1.3.2 Research by the PRST: Post-approval changes (ICH Q12)

Research is underway currently by Ramnarine (Ramnarine, 2020) examining how an effective PQS could transform post-approval change management to, in turn, solve the continual improvement and innovation challenge faced by the industry. Among other challenges, this research also looks at how knowledge and knowledge management enable post-approval changes (PACs). Figure 2-10 is a representation of how product knowledge grows across the product lifecycle. In principle there will always be more knowledge available than is captured in the CTD (Common Technical Document, i.e., the regulatory filing).

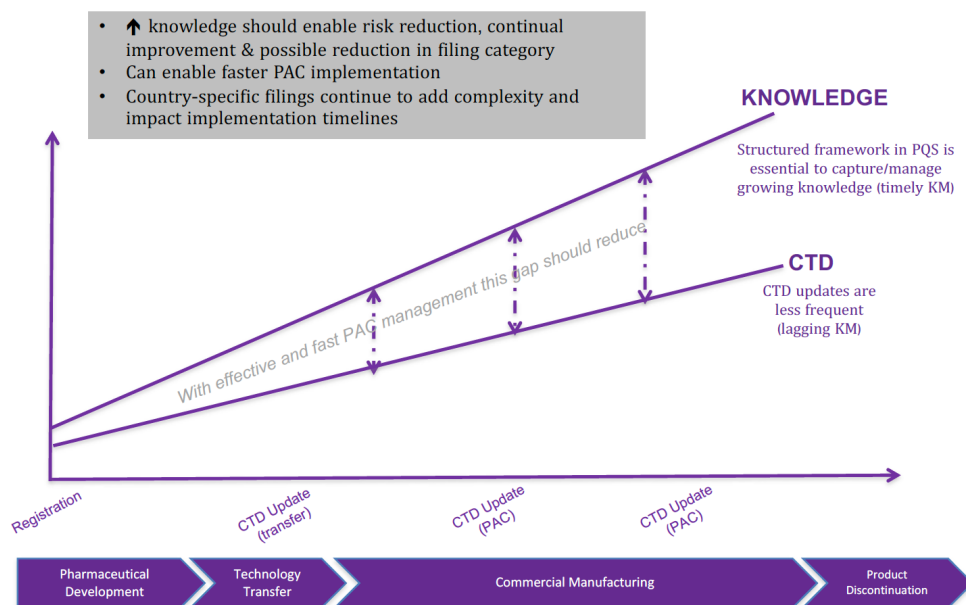


Figure 2-10 – Maintaining product knowledge in the PQS vs. regulatory filings (Ramnarine, 2020)

‘Timely knowledge management’ is required to manage this knowledge effectively and to in turn be able to apply a firm’s knowledge to identify the need for a change, to manage the risk associated with the change, implement the change and to ensure the change was successful. Of note, KM was identified as a top priority to gain regulatory flexibility. Ramnarine et al. explain the role of KM in maintaining a state of control, facilitating continual improvement and management of post-approval changes through the PQS in Figure 2-11 (Ramnarine *et al.*, 2019).

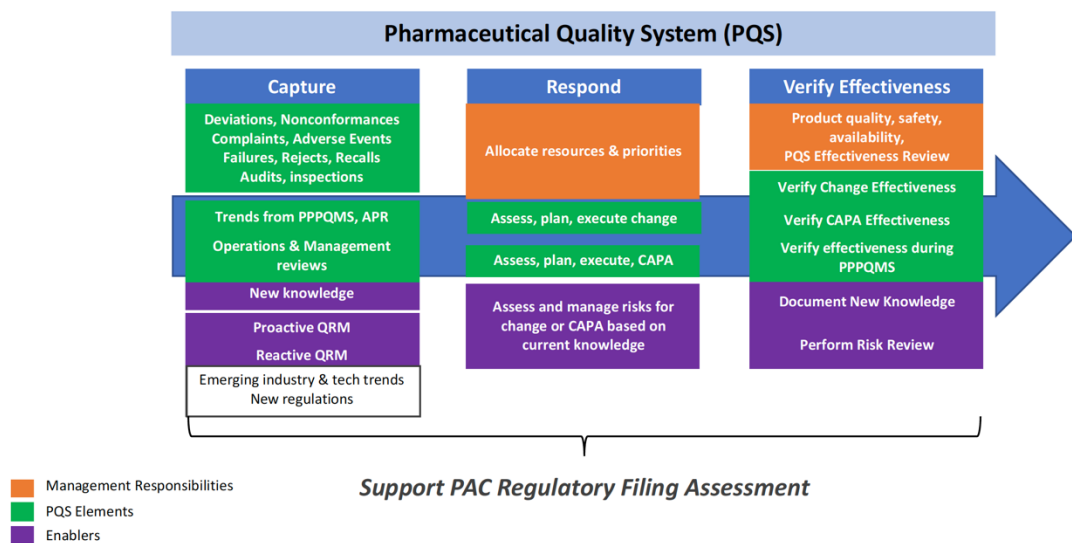


Figure 2-11 – Managing post-approval changes through the PQS (Ramnarine et al., 2019)

2.1.3.3 Additional research & contributions by the PRST

Additional work by the PRST is embedded and referenced throughout this research study, including those works carried out by the researcher summarised elsewhere in this thesis and the work of PRST colleagues such as Kevin O’Donnell (O’Donnell, 2020). In addition, the PRST has published multiple monographs since 2018 on the topics of QRM and/or KM.

2.1.4 Knowledge management – Knoco 2020 benchmarking survey

The majority of significant developments since the completion of Kane’s research and the start of this research study have been captured in other sections within this literature review. One additional development was the issuance of the *Knoco 2020 Global Survey of Knowledge Management* and associated report (Knoco, 2020). Surveys were also conducted by Knoco in 2014 and 2017 and these are reviewed in detail in the

literature review contained in Kane’s thesis (Kane, 2018), of which select highlights are shared here. These important surveys are the only one of their type and breadth but are industry-agnostic and there is not a specific category for pharmaceuticals, so sector-specific assessments of results or changes over time for pharmaceutical are not possible. Further, the goals of KM across sectors are not as focused on the quality management system as there are many additional drivers for KM in organisations. Regardless, these data summarised below are useful to understand a bigger focus on KM at the global level. Given the sector choices provided by the survey, the researcher anticipates most participating organisations in the pharmaceutical sector would have labelled themselves as *Professional, Scientific and Technical Services* or *Manufacturing*.

The 2020 survey received a total of 453 responses, up from 427 in 2017 and 386 in 2014. The trend of KM importance is rising in a significant percentage of responses at 71%, with a small 5% minority indicating the importance of KM is on the decline. The survey also assessed cultural issues that act as barriers to KM programs, which are important clues to a transformation change management focus in support of KM. Results are summarised in Figure 2-12, and show that the leading barrier to KM programmes was short-term thinking followed by lack of openness to sharing.

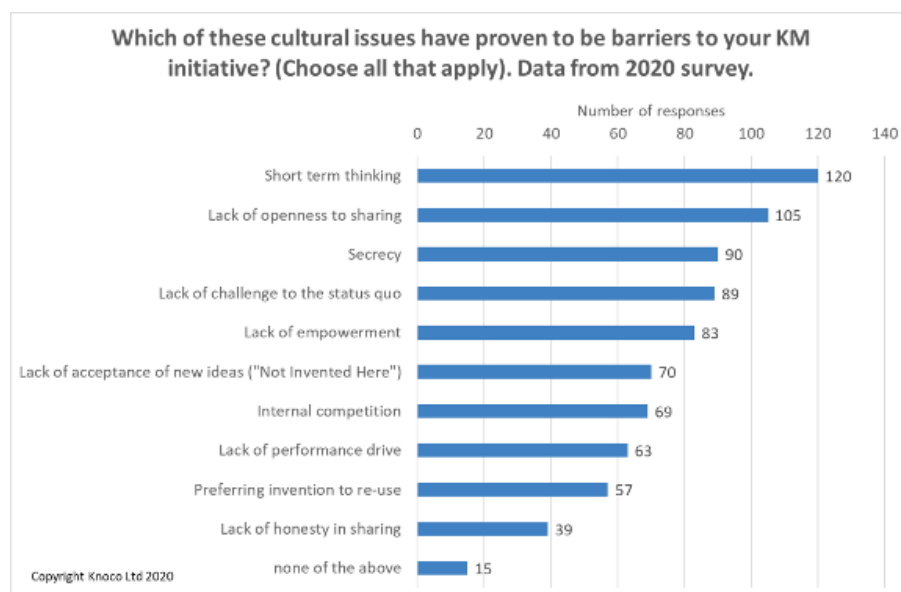


Figure 2-12 – Cultural issues acting as barriers to knowledge mgmt. (Knoco, 2020)

Many additional results are available in the Knoco survey (Knoco, 2020). These specific results were selected by the researcher based on their relevance to this research effort and anticipated outcomes.

2.1.5 Summary – knowledge management across the product lifecycle

Reviewing regulatory expectations in aggregate for management of product and process knowledge across the lifecycle, the researcher draws the following conclusions:

- There are broad and consistent expectations across an array of authoritative sources for product and process knowledge to be managed proactively across the product lifecycle
- Increased knowledge is the means to drive continual improvement
- Knowledge lies in multiple formats, including documents (explicit knowledge), experience (tacit knowledge) and an array of sources which in reality are a mix of explicit and tacit knowledge, including development history, change history (with rationale), and problem history with associated resolutions, among others
- These knowledge sources are relevant to the given product, but may be leveraged across products as ‘prior knowledge’
- Knowledge leads to understanding and risk reduction which in turn leads to improved patient outcomes. Knowledge should not only include ‘what works’ for a given product or process but also should include learning from ‘failures’ (e.g., experiments with unexpected outcomes)
- There are several linkages between KM and QRM (discussed further in section 2.2)

Yet, In the opinion of the researcher, it appears there is a general lack of industry guidance for KM, especially when compared to available literature on QRM. It is noted that there has been recent activity which may be starting to address this gap.

There are potentially exciting developments on the research front that will continue to raise awareness of the need to improve KM, including this research study. It is worth mentioning the annual Knowledge Management Conference held by APQC is alive and well and would have hosted it’s 25th Anniversary Event in May of 2020 (APQC, 2020), although regrettably cancelled due to the COVID-19 pandemic. The researcher has been a regular attendee and a steering committee member for 3 of the past 5 years,

and attendance at this conference has continued to grow. This conference is a premier event for KM globally and is an annual event which draws approximately 400 attendees across a highly diverse industry base. The conference is on track to resume in October of 2021.

2.2 Quality Risk Management and Knowledge Management

A detailed literature review on QRM and KM was conducted as part of this study with two primary focus areas as outlined below. This literature review was published in a peer-reviewed journal, the *Journal of Validation Technology* (Lipa, O'Donnell and Greene, 2020c), with the findings summarised below.

The first area of focus of the literature review was an exploration of available literature to understand how QRM and KM have been related in other studies and other industries. The review strongly suggested that the interplay between managing risk and managing knowledge is not new. For the last 20+ years this has been a topic of discussion spanning finance, legal, information technology, aerospace, corporate risk management, military, and other domains. The findings are consistent, in that there is a direct relationship between knowledge and risk – more knowledge one has leads to increased understanding and decreased uncertainty – and therefore to lower risk.

The second area of focus of the literature review was on regulatory guidance, examining the relationship between *risk* and *knowledge* in the guidance as a means to better characterise any interdependency between risk and knowledge, as well as RM and KM. The review suggest that collectively the themes of knowledge and risk, along with KM and RM as structured means to manage each, are prevalent and persistent across the diverse set regulatory literature reviewed. The review also sought to look beyond explicit and obvious descriptions stating how RM and KM are linked. The intent was to examine the more subtle instances of how knowledge and risk are connected, in addition to KM and RM, even though these latter terms are used less frequently (especially KM). Further, the review also reflected on the FDA's vision of science and risk-based quality for the 21st century (US FDA, 2002) given the inseparability of

knowledge and science. According to the WHO guideline on Quality Risk Management (WHO, 2013), an 'effective and secure knowledge management system' is crucial to quality risk management. This WHO guideline also highlights the expectations for using not only documented knowledge (i.e., explicit knowledge), but also establishes the expectation for using the knowledge 'in the heads of people' where experience and expertise are critical (i.e., tacit knowledge).

As this literature review demonstrated, knowledge and risk bear a clear relationship, with **knowledge being recognised as both an input and an output to quality risk management**. This leads to greater control of risks to quality through increased understanding. The pairs are each interwoven: knowledge & risk, and knowledge management & risk management.

Furthermore, a key concept is that 'risk varies inversely with knowledge' (Fisher, 1907). The researcher challenged this as a potential over-simplification and asserted that risk varies inversely with knowledge *applied*, indicating the need for the knowledge to be created, identified, stored, accessible and 'flow' on demand to when and where it is needed. The researcher developed the following figure (Figure 2-13) to illustrate this point, that risk is a function of knowledge application, and knowledge application is in turn a function of knowledge flow, availability, capture (and more). Therefore, risk is also dependent on knowledge flow, availability, capture (and more), highlighting the need for robust KM processes to maximise risk reduction.

Risk varies inversely with Knowledge Applied

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

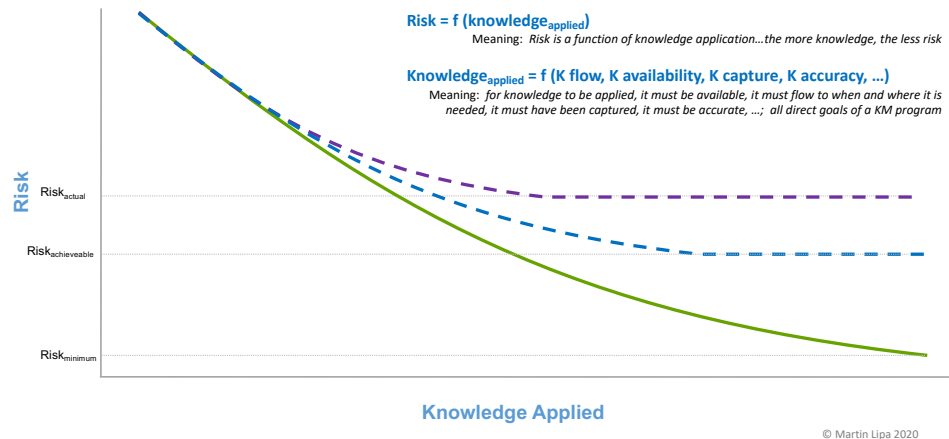


Figure 2-13 – Risk varies inversely with knowledge applied

Further implications from this literature review will be explored in Chapter 5 of this thesis.

2.3 Technology Transfer and Knowledge Management

The next section of the literature focuses on KM in technology transfer.

2.3.1 Regulatory guidance

Regarding technology transfer, **ICH Q10** (ICH, 2008) states technology transfer activities including new product transfers during development through manufacturing and transfers within or between manufacturing and testing sites for marketed products are both in scope of ICH Q10.

In section 3.1 on *Lifecycle Stage Goals*, ICH Q10 provides arguably a pivotal goal statement for technology transfer being primarily about *knowledge transfer* as follows (emphasis in bold added by the researcher):

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement.

ICH Q10 proceeds to provide application insights for each lifecycle stage (i.e., pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation) for each of the four PQS elements, including (i) Process Performance and Product Quality Monitoring System, (ii) Corrective Action and Preventive Action (CAPA) System, (iii) Change Management System and (iv) Management Review of Process Performance and Product Quality. Key points relating to technology transfer include strong interdependencies with KM practices, including that technology transfer should be a learning opportunity to grow knowledge about a product ('Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy'), that acquired knowledge should be applied both feedback and feedforward basis ('CAPA can be used as an effective system for feedback, feedforward and continual improvement') and that it sets up the role of knowledge management to manage explicit knowledge for change management ('the change management system should provide management and documentation of adjustments made to the process during technology transfer activities').

In the introduction of **Annex 7 to the WHO guideline on Transfer of Technology in Pharmaceutical Manufacturing**, the following principle is presented citing the expectation for management of explicit and tacit knowledge as part of technology transfer (WHO, 2011) (emphasis in bold added by the researcher):

*Transfer of technology is defined as "a logical procedure that controls the **transfer of any process together with its documentation and professional expertise** between development and manufacture or between manufacture sites". It is a **systematic procedure that is followed in order to pass the documented knowledge and experience gained** during development and or commercialisation to an appropriate, responsible and authorised party.*

Further in this guideline, KM is mentioned but not specifically defined:

In the event that the RU [receiving unit] identifies particular problems with the process during the transfer, the RU should communicate them back to the SU [sending unit] to ensure continuing knowledge management.

Management of knowledge is clearly inferred throughout the document, including in section 5 where process history, reasons for changes, and problems and outcomes are examples of types of knowledge referenced. Chapter 8 of the WHO guideline includes a list of documentation (explicit knowledge) to be transferred.

2.3.2 Industry guidance (pharmaceutical industry-specific)

This section includes a review of pharmaceutical *Industry Guidance* literature from industry associations and other authorities with a focus on technology transfer. The scope of literature surveyed includes:

- WHO Guidelines on Transfer of Technology in Pharmaceutical Manufacturing – Annex 7 (WHO, 2011)
- NIHS Japan: Guideline for Technology Transfer (NIHS, 2005)
- ISPE: Good Practice Guide: Technology Transfer, 2nd Edition (ISPE, 2014)
- ISPE: Good Practice Guide: Technology Transfer, 3rd Edition (ISPE, 2018)
- PDA: Technical Report No. 65: Technology Transfer (PDA, 2014b)
- PDA: Technical Report No. 65: Technology Transfer¹⁶
- PDA Technology Transfer Industry Survey (via Interest Group Report out at PDA 2019 Annual Meeting and 2019 Technology Transfer Industry Survey (Seymour *et al.*, 2019)
- Technology and Knowledge Transfer - Keys to Successful Implementation (Gibson and Schmitt, 2014) (published by PDA, although not an official Technical Report)

In general, these guidance present frameworks, processes, and considerations for conducting technology transfer from which individual companies construct their respective technology transfer business processes. Of particular interest in this review is an evaluation of whether the guidance documents include guidance on *expectations* for knowledge management and knowledge transfer, as well as any further guidance on *how* this might be accomplished. The first step was an assessment of the extent to which key concepts including **knowledge transfer**, **knowledge management** and **tacit knowledge** (and synonym ‘**know-how**’) are present.

¹⁶ This PDA Technical Report is currently under revision, but the revision has not been published in time for inclusion in this thesis. The researcher has been invited to provide feedback on the upcoming revision which is further explained in section 10.3.

A further qualitative assessment of the literature was conducted by the researcher on how well these documents introduced these concepts, including how well they are collectively **explained**, whether they **provided illustrative examples**, and whether they **provided guidance / tips on 'how'**. Details are provided in the corresponding paper (Lipa, Kane and Greene, 2019), and are summarised by the researcher as follows:

- Technology transfer guidance is typically very '**document-centric**' (i.e., focused on explicit knowledge)
- Knowledge management, with a focus on explicit knowledge, is identified in guidance but is **lacking in practical application** as the researcher observed the following:
 - **Lack of supporting principles or guidance on how** to manage or transfer knowledge effectively
 - This absence of guidance may be starting to change, but perhaps still not enough or fast enough given lag time for industry awareness, interpretation, and application
- '**Tacit**' knowledge is **rarely recognised** as a source of knowledge, nor is there guidance on how to manage or transfer
- Technology transfer risks of failure **do not acknowledge** concepts of **insufficient knowledge transfer or availability in the future**.

Regarding ISPE guidance on technology transfer, the second edition of the Good Practice Guide (ISPE, 2014) was included as a baseline for comparison against third edition, in order to evaluate any changes over time. The third edition (ISPE, 2018) lists five key rationale for the revision, one of which is 'Recognition that knowledge management is a critical component of effective technology transfer...'. It is clear in the results summarised by the researcher, the presence of knowledge management and related concepts has been significantly strengthened beyond a starting baseline from the second edition, suggesting recognition of the need to provide further details in guidance.

Regarding PDA guidance on technology transfer, the *PDA Tech Transfer Interest Group* at the 2019 PDA Annual Meeting shared the results of a recent survey which they conducted on technology transfer (Seymour *et al.*, 2019). The survey was intended to

assess the current practices and future needs for improving the technology transfer process as an input to a planned revision of PDA Technical Report 65, Technology Transfer (PDA, 2014b). The survey covered:

- Demographics
- Types of Technology Transfer Performed
- The Technology Transfer Process
- Use of Multi-Disciplinary Teams
- Technology Transfer Tools
- Challenges

The researcher attended the conference session where the PDA Technology Transfer survey results were presented (Haas, 2019) and the results were subsequently published by PDA (Seymour *et al.*, 2019). In response to the survey question “What are the top three areas for which a PDA guidance would enhance technology transfer?”, approximately 40% of respondents included *Knowledge Management* as one of their top 3 priorities as illustrated in Figure 2-14.

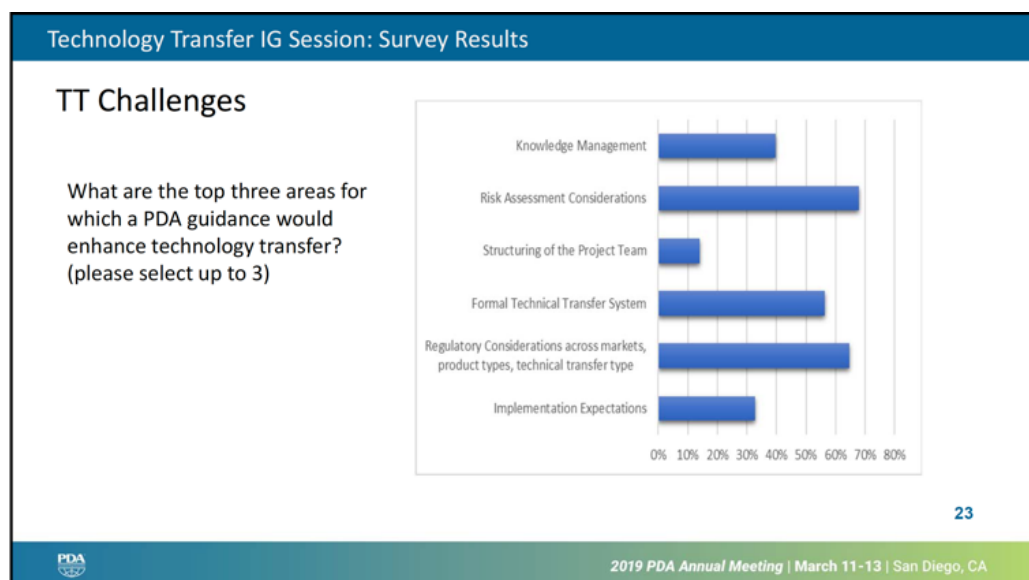


Figure 2-14 – PDA technology transfer survey (Haas, 2019)

In the opinion of the researcher, there are also underlying correlations with KM in many other survey questions. For example, when asked “What do you see as your biggest obstacles for technology transfers?”. The top two replies were *Communication/*

Collaboration and Timeliness of Deliverables. While not specifically cited nor labelled as a knowledge transfer challenge, it is highly likely that structured knowledge transfer would dramatically address these obstacles. Notably, *Risk Assessment Considerations* was the most frequent challenge area, identified as a challenge by nearly 70% of the respondents. This suggests an indirect dependency on knowledge and knowledge management. Risk and knowledge are interdependent, as will be explored in Chapter 5.

Of note, during the PDA conference, the discussion on KM in the Technology Transfer Interest Group (IG) session focused heavily on a '*master plan*' for KM which primarily focused on documents and information with no references to tacit knowledge, 'know-how', learning from failures, experience, or any other non-explicit knowledge management inferences. These master plans are useful in that they highlight key activities which generate knowledge, but they do not expressly identify tacit knowledge nor assess the effectiveness of knowledge transfer.

There was also a link established at the PDA conference between KM and 'soft skills' as shown in Figure 2-15. Some of these could perhaps be extended to traditional KM practices (like a community of practice to communicate broadly). However, it is the opinion of the researcher that in the main, these items tagged as KM 'soft skills' as proposed by PDA are indeed important but are generally not KM-related skills. The researcher sees this as a risk of possible confusion on the intent behind KM, especially if this is carried through to the revision of *Technical Report 65, Technology Transfer* ongoing in 2021.

Technology Transfer IG Session: Framework

Knowledge Management: Soft Skills

Successful cross-functional interaction takes leadership with the following traits to facilitate communication and teamwork

- Adaptability
- Team motivator and leader
- Expressing team milestones as part of the business goals
- Ability to communicate at all levels of an organization
- Communication of complex issues
- Some knowledge of all functional areas to develop relevant project plan, determine critical path items, and resource needs
- Facilitation/ negotiation skills

COMMUNICATE.....COMMUNICATE.....COMMUNICATE

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PDA 2019 PDA Annual Meeting | March 11-13 | San Diego, CA

Figure 2-15 – Knowledge management and ‘soft skills’ (Haas, 2019)

In addition, PDA has published an insightful book on technology transfer, aptly titled *Technology and Knowledge Transfer: Keys to Successful Implementation and Management* (Gibson and Schmitt, 2014). Aside from providing an excellent history and outline of technology transfer, it begins to describe knowledge transfer elements. Although many of the KM-related elements are somewhat information technology centric (i.e., IT system), there are supportive concepts for KM (including that of tacit knowledge) with multiple references to *knowledge transfer*, *knowledge management*, ‘*know-how*’ and how culture can support knowledge transfer. Although also a PDA publication, it is not evident to the researcher whether this resource and associated concepts within are being pulled into the revision of the PDA Technical Report on technology transfer as it remains to be seen what emerges in the final document.

2.3.3 Exploring the foundations of Technology Transfer and Knowledge Transfer

A literature review was conducted to explore the current state of knowledge transfer during technology transfer, in general and in the pharmaceutical industry, including associated challenges, principles, and models or frameworks.

2.3.3.1 Technology transfer

It was not so long ago in 2003 when Kremic (Kremic, 2003) asserted technology transfer does not have a universal meaning but rather has broad connotations and is very contextual. Shortly after in 2004 Reisman (Reisman, 2005) stated ‘technology transfer is an emerging field of knowledge in which institutional interest is rapidly expanding.’ Cases are noted in use by firms for competitive advantage, governments towards economic progress and social development, universities for commercialisation and licensing of research outputs (Audretsch, Lehmann and Wright, 2014; de Wit-de Vries *et al.*, 2019) and for government research institutions to give access to new technologies to taxpayers (Schacht, 2012). Reisman continued:

As is often the case in an emerging area or discipline, its descriptive as well as normative theories and data available are fragmented and disjointed. There is no general theory, model or structure for the field¹⁷...the very definition of technology transfer differs across the many disciplines addressing technology transfer, and the scope of transfer has rarely been delineated or systematically analysed. Currently, transfer can be understood only in a limited way from a strict disciplinary framework and/or a specific aspect.

Well over a decade has passed and there is little evidence to this changing significantly. Dubickis and Gaile-Sarkane (Dubickis and Gaile-Sarkane, 2017) assert that the concept of technology transfer is not easy to define, citing a study from Sazali and Raduan in 2011 which identified nearly 30 different viewpoints on technology transfer (Wahab, Rose and Suzana, 2012). Ismail *et al* in 2016 (Ismail, Hamzah and Bebenroth, 2018) defined technology transfer as ‘the process of transferring or disseminating technology from its origin to a wider distribution, to more people and places.’

Specific to the pharmaceutical industry, the definition of technology transfer also appears – surprisingly given the highly regulated nature of the industry – not singularly defined. The definition is stated differently across a variety of less formal channels

¹⁷ The researcher found this lack of maturity very surprising, having assumed that the practice of technology transfer would have been more established and consistent. This was a key learning for the researcher. Furthermore, Reisman’s quote noted here could perhaps similarly be applied to knowledge management, perhaps just a few years behind technology transfer in its own maturity journey

including conference presentations, articles by consultants and marketing materials. The definitions of technology transfer identified from seemingly authoritative sources are as follows:

- WHO guidelines on transfer of technology in pharmaceutical manufacturing (WHO Technical Report Series, No. 961, Annex 7) (WHO, 2011): ‘a logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacturing or between manufacturing sites.’
- Pharmaceutical Research and Manufactures of America’s (PhRMA) Quality Technical Committee in 2003 defined technology transfer as: ‘The body of knowledge available for a specific product and process, including critical-to-quality product attributes and process parameters, process capability, manufacturing and process control technologies, and quality systems infrastructure.’ (cited by Millili (Millili, 2011))
- ICH Q10 (ICH, 2008) states the goal of technology transfer rather than labelling it a definition. This seems to be a commonly adopted working definition by the industry: ‘The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation.’

This latter was used as the definition of technology transfer in a 2015 paper titled *Overview of Best Practices for Biopharmaceutical Technology Transfers* (Abraham *et al.*, 2015), authored by a team across six biopharmaceutical companies. The authors explain in their paper, technology transfer is a key foundational component in product commercialisation and is more than just the transfer of documents; it relates to all aspects of the transfer of knowledge and experience to the commercial manufacturing unit to ensure consistent, safe, and high-quality product. They further assert that understanding how to streamline and improve technology transfers is complicated by companies using different terminology and ways of working regarding technology transfer. The authors define key terminology associated with technology transfer and propose a process overview with key activities and milestones, from which the researcher has re-framed from a table to the process view show in Figure 2-16.

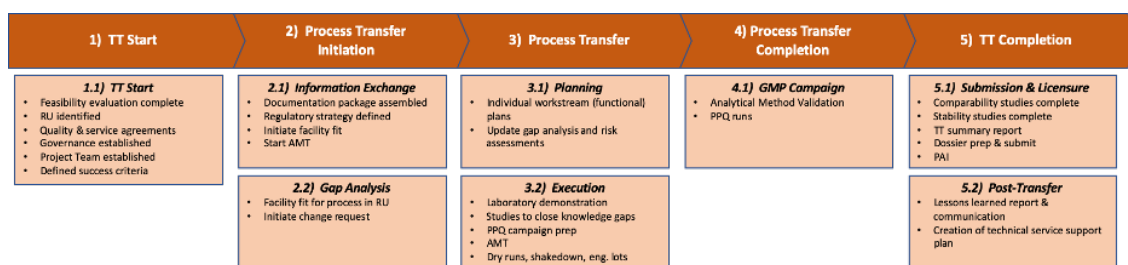


Figure 2-16 – Key activities and milestones in biopharmaceutical technology transfer

2.3.3.2 Knowledge transfer

Kwan et al. (Kwan and Cheung, 2006) describe knowledge transfer as ‘the process through which one unit (e.g., group, department, or division) is affected by the experience of another.’ In addition, they note that knowledge transfer is treated by most researchers as a black box. They propose that a process view that emphasises the sequence of events would provide insights on the nature of the inner workings of knowledge transfer. However, few researchers have explicitly suggested a process model for the knowledge transfer, and of the conceptual models and frameworks found, they observed them to be diverse and based on theories from various disciplines. Kwan et al. subsequently proposed a knowledge transfer management system (KTMS) to support needs across the different stages of their proposed knowledge transfer process model (*Motivation, Matching, Implementation, Retention*) in which appropriate knowledge management tools were applied at each stage of the process.

Liyanage et al. (Liyanage *et al.*, 2009) describe knowledge transfer as ‘the conveyance of knowledge from one place, person or ownership to another.’ Successful knowledge transfer means that transfer results in the receiving unit accumulating or assimilating new knowledge. A thorough review of literature reveals that many authors and researchers have failed to provide a clear-cut definition for knowledge transfer, and at times, it has been discussed together with the term “knowledge sharing.”

Dixon (Dixon, 2017) suggests ‘a general call to encourage more knowledge sharing or transfer is not very effective because there are many ways to transfer knowledge.’ Dixon proceeds to propose a knowledge transfer framework based on two questions,

(i) 'What is the transfer problem you are trying to solve?' and (ii) 'What type of knowledge do you want to transfer?' From these inputs, Dixon proposes how the knowledge can be harvested or captured, and how the knowledge can then be transferred.

Ward et al. (Ward, House and Hamer, 2009) conducted a study of existing models and frameworks for knowledge transfer and inventoried 28 generalised frameworks in the literature and identified five common components. This led the authors to the proposal of a conceptual framework embodying those five common components as:

- i. the problem
- ii. the knowledge
- iii. the context barriers or supports
- iv. the interventions
- v. the utilisation

The model developed by Liyanage et al. is presented as a figure (Liyanage *et al.*, 2009) and is reproduced here in Figure 2-17. This model highlights the need to address a number of questions prior to the implementation of a transfer mechanism:

- Who needs the knowledge (receiver)?
- What units (in the supply chain) are involved in the knowledge transfer process?
- What is the most appropriate "source" to acquire the required knowledge (awareness)?
- What is/are the type(s) of knowledge to be transferred?
- How should it be transferred (modes of knowledge transfer)?
- What are the factors that will influence on the process of knowledge transfer and what is their level of impact?
- What can we do to enhance the factors that positively influence on the process of knowledge transfer and what can we do to avoid/lessen the impact of the factors that negatively influence on the process of knowledge transfer?
- What mechanisms should be used by the receiver to ultimately utilise the knowledge?
- Did the knowledge transfer process successfully achieve its goals (performance measurement)?

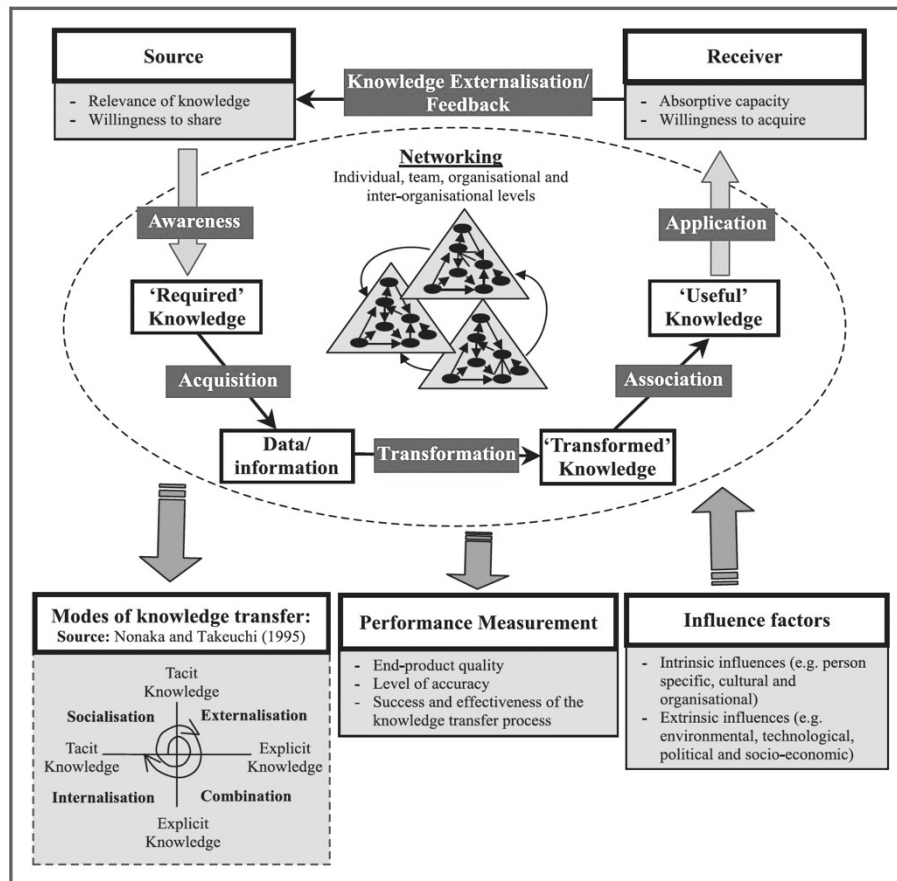


Figure 2-17 – Knowledge transfer process model (reproduced) (Liyanage et al., 2009)

Liyanage et al. (Liyanage *et al.*, 2009) assert that knowledge leads to organisational value when it is used to effectively make decisions, solve problems, and produce effective performance. Thus, successful application of knowledge during a knowledge transfer process usually results in one or more of the following:

- reduced errors (e.g., by not repeating mistakes)
- improved quality (e.g., by using best of breed practices)
- speeding up decision making (e.g., by getting better cross-functional coordination)
- lower costs (by quickly identifying expertise) or provide value for money
- speeding up training (e.g., by attending to common mistakes and learning from best practices)
- learning and innovation

Specific to tacit knowledge considerations, Foos et al. (Foos, Schum and Rothenberg, 2006) explored the factors which influence the transfer of tacit knowledge between

partners based on a qualitative and quantitative analysis, including a study of three companies charged with integrating external technology. They found that trust, early involvement, and due diligence influence the extent of meeting technology transfer expectations and tacit knowledge transfer expectations. They also assert that the subject of tacit knowledge transfer, content, and process is poorly understood and lacking formal process. To explore this idea further they carried out a survey on knowledge transfer. About two-thirds of their survey respondents indicated they were attempting to integrate tacit knowledge, while **92% reported no formal process for tacit knowledge transfer**. Foos et al. (Foos, Schum and Rothenberg, 2006) also suggested there is clear evidence that intentional management mechanisms for tacit knowledge management are needed, and that they will differ from those for more explicit types of knowledge. Finally, while managers and project leaders saw the value of tacit knowledge, there were different perceptions of the goals of successful knowledge transfer and a lack of processes to manage its process. They noted project managers may feel they have tacit knowledge transfer in hand, but they have not managed to transfer the knowledge needed for long-term product management.

Malik (Malik, 2002) highlights 'know-how' must be learned and acquired. The difficulties associated with embedded 'know-how' transfer they identified include:

- Knowledge on how to use a technology
- What the technology is capable of
- The tacit components of knowledge embedded in the technology
- Difficulties in interpreting technological codified knowledge

Kumar and Ganesh (Kumar and Ganesh, 2009) state knowledge transfer is not a complete replication of knowledge in a new location; rather, it involves the modification of some existing knowledge to a different context, 'what is transferred is (usually) not the underlying knowledge but rather applications of this knowledge in the form of solutions to specific problems.' This insight further highlights the need for interpretation and context to be shared (tacit knowledge).

The process of knowledge transfer is not, per se, a mere transfer of knowledge, (Seaton, 2002) as cited by Liyanage et al. (Liyanage *et al.*, 2009), it requires an additional type of knowledge: the knowledge about how to transfer knowledge. As an example, instead of saying ‘this is what I know,’ the process of knowledge transfer goes one step further to say, ‘this is what my knowledge means for you.’ Thus, contextualisation is important for knowledge transfer to be effective.

Rathore et al. (Rathore *et al.*, 2017) conducted a study specific to the biopharmaceutical industry, looking at the role of knowledge management in development and lifecycle management with a specific focus on knowledge management tools to support Quality by Design (QbD) related tasks. Their paper acknowledges the shift towards extraction of ‘know-how’ and tacit knowledge as opposed to classic explicit ‘data capture’ approaches which represent a new direction for the field [of knowledge management], however the authors did not address this further in their paper. They also acknowledged that knowledge from transfer activities is not sufficiently covered by knowledge management current tools, for which they provide a functional classification.

2.3.3.3 Knowledge transfer and technology transfer

Galbraith (Galbraith, 1990) studied 32 ‘core manufacturing technology transfers’, including pharmaceutical technology transfers, examining success of the transfers and other factors such as sources of cost and lost productivity. Galbraith noted that studies of manufacturing technology transfer underline two important facts: (i) any type of technology transfer involves not only the movement of equipment and people, but also the flow of critical information or ‘know-how’ between donor and recipient organisations; and (ii), there are significant direct costs attached to the transfer and management of this knowledge. The direct costs associated with transfers are twofold: resource costs to perform the transfer; and productivity and ‘know-how’ loss. On studying the 32 transfers, Galbraith reported the initial percentage productivity loss experienced by the recipient facilities ranged between a low of 4% to a high of 150%, averaging a 34% initial productivity loss. The time it took to recover lost productivity ranged between 1 month to 13 months, however 10 of the transfers never reached pre-

transfer productivity levels or were considered failures for other reasons (31% failure rate). Galbraith (Galbraith, 1990) associated a set of risks for technology transfer success, including misplaced documents, distance between facilities, the recipient's previous experience with incoming transfers, and transferring complex process in early stages of development.

Malik (Malik, 2002) asserted that a number of knowledge transfer models for technology transfer have not recognised fully that intra-firm transfers are two-way iterative processes and not simply one-way linear processes. Malik then proposed an interactive model highlighting factors influencing the technology transfer process (e.g., culture of trust), the mode of transfer and a feedback loop. Liyanage et al. (Liyanage et al., 2009) have reinforced the need for a feedback loop and incorporated it into their proposed model (Figure 2-17).

Gorman (Gorman, 2002) in his paper *Types of Knowledge and Their Roles in Technology Transfer* presents a taxonomy of knowledge with respective roles in technology transfer, distinguishing between four types to refine the distinction between tacit and explicit knowledge. The four types are:

- Information (what)
- Skills (how)
- Judgment (when)
- Wisdom (why)

Table 2-2 created by the researcher as a summary of the article text provides an overview of each, along with the related types of each explicit and tacit knowledge.

Table 2-2 – Types of knowledge and their role in technology transfer (Gorman, 2002)

Type of Knowledge	Description	Explicit	Tacit
Information (what)	Declarative, knowing that	<i>Information, facts</i>	<i>Contextualisation of facts, knowing when and where valid</i>

Type of Knowledge	Description	Explicit	Tacit
Skills (how)	Procedural, knowing how	<i>Algorithms</i>	<i>Heuristics, rules of thumb</i>
Judgment (when)	<ul style="list-style-type: none"> • Recognising a problem is similar to one whose solution path is known, knowing when to apply a particular procedure • Accumulated facts structured in ways that facilitate problem solving • Ability to recognise cues • ‘Feel’ for what will or won’t work • Result of accumulated implicit learning 	<i>Rules</i>	<i>Mental models, case-based experience</i>
‘Why’ (wisdom)	<ul style="list-style-type: none"> • The ability to reflect on status quo, question prevailing mental models and evolve • Requires moral imagination (i.e., to step outside one’s self-view, assumptions and bias and be able to creatively envision new possibilities) 	<i>Codes (e.g., code of conduct)</i>	<i>Moral imagination</i>

Barros et al. (Barros *et al.*, 2020) conducted a comprehensive literature review of the interaction between knowledge management and technology transfer published in 2020 in an attempt to better define the context of the relationship between the concepts. They found that most studies where knowledge management and technology transfer co-occur focused on the private sector and on technology transfer for attaining innovation, customer orientation and acquiring technological abilities. The university-industry relationship was also observed, in which universities create and transfer knowledge to support industry goals. There were many references to the need and importance of knowledge transfer although no information on knowledge transfer frameworks and no specifics to the pharmaceutical industry were given.

2.3.4 Summary – technology transfer and knowledge transfer

Given the subject literature, the researcher drew several conclusions from the review.

- There exists regulatory and industry guidance for how to do technology transfer that include expectations for knowledge management, yet these guidances are very general in nature, provide no direction on ‘how,’ and largely neglect tacit knowledge.
- Technology transfer itself is a relatively ‘young’ practice, lacking in clear definition – including for the pharmaceutical industry – and is highly contextual.

- Knowledge transfer models identified are quite academic and theoretical; importantly they raise underlying drivers such as motivations, capacity and other factors but neglect to define a pragmatic and deployable framework, nor provide any information on the ‘how.’
- Tacit knowledge (‘know-how’) is recognised as critical for overall successful knowledge and technology transfer, yet there appears to be a general lack of processes for formal tacit knowledge transfer. People know it’s important but don’t know how to do it.

Notably, although there were selected pharmaceutical industry references in aggregated studies involving technology transfer and knowledge transfer cited above (Galbraith, 1990; Barros *et al.*, 2020), there was no evidence of a focus on knowledge transfer frameworks (or models or processes) for pharmaceutical technology transfer, aside from documentation turnover lists (WHO, 2011; PDA, 2014b; ISPE, 2018).

Given the highly knowledge-dependent definitions of pharmaceutical technology transfer, the dependence on and transfer of both explicit knowledge (e.g., documents) and tacit knowledge (e.g., expertise) is central to the intent and paramount to the success of a pharmaceutical technology transfer. Bruce Davis, an industry subject matter expert on technology transfer (e.g., as demonstrated by leading the development of the current ISPE Good Practice Guide on Technology Transfer (ISPE, 2018)) presented a paper entitled an *Introduction to Technology Transfers, Basics & Principles* at the ISPE 2019 Annual Meeting (Davis, 2019) which the researcher attended in person. Davis’ presentation focused heavily on knowledge management and its importance to technology transfer, citing ICH Q10 (ICH, 2008). Davis shared his professional insights during his presentation, including:

Understanding the knowledge and really solid project management coming together is what makes for a successful technology transfer ... If you don’t have product & process understanding you cannot do a successful technology transfer.

Lastly, as stated by Malik (Malik, 2002), ‘technology transfer represents one of the most knowledge intensive and problematic relationships in a firm.’ Yet there is no evidence the pharmaceutical industry has solved the knowledge transfer conundrum through a

framework, guidance or other visible progress, even though the success of the industry is highly dependent on it.

2.4 Domains of knowledge: knowns and unknowns

Where knowledge is involved, a majority of the literature discussed to this point is about what is known, or what one might describe as *known-knowns*. The researcher has an interest in broadening this lens to understand the opportunity to explore what is unknown as part of a more holistic approach to transferring knowledge and managing risk.

Drew in 1999 (Drew and Whitehill, 1999), in support of how knowledge management supports strategy development, published a knowledge portfolio matrix along two simple axes: *knowledge content* and *knowledge awareness*. The knowledge content axis represents ‘do we know (or not)?’, while the knowledge awareness axis represents ‘are aware that we know it (or not)?’ (Figure 2-18).

Knowledge Awareness	1. What We Know We Know	2. What We Know We Don't Know
	<i>Emphasis:</i> knowledge sharing, access and inventory. <i>Tools:</i> e.g. benchmarking, communities of practice.	<i>Emphasis:</i> knowledge seeking and creation. <i>Tools:</i> e.g. R&D, market research, competitive intelligence.
	3. What We Don't Know We Know	4. What We Don't Know We Don't Know
	<i>Emphasis:</i> uncovering hidden or tacit knowledge. <i>Tools:</i> e.g. knowledge maps, audits, training, networks.	<i>Emphasis:</i> discovering key risks, exposures and opportunities. <i>Tools:</i> e.g. creative tension, audits, dilemmas, complexity science.
	Knowledge Content	

Figure 2-18 – Knowledge portfolio (Drew and Whitehill, 1999)

The researcher finds this a helpful thought model to use to think more comprehensively about knowledge management, inclusive of knowledge transfer, and risk management across the entire product lifecycle as it consciously prompts a reflection on recognised gaps in our knowledge (i.e., “we don’t know what will happen if ...”).

Others have followed similar thinking such as Browning (Browning and Ramasesh, 2015) who proposed that many unknowns are knowable and through a set of processes called directed recognition, risk could be reduced. Many of these processes, in the opinion of the researcher, are in knowledge management or closely related processes and related behavioural approaches. Marshall et al. (Marshall *et al.*, 2019) also explored ‘four states of risk forecasting knowledge,’ following the same four quadrant categories as Drew, with a powerful model to decrease risk through increasing one’s risk radar.

The researcher synthesised these insights to create a representation (Figure 2-19) into a four-quadrant grid of *knowns* and *unknowns*. The labels in each of the boxes in Figure 2-19 form a helpful thought model to simplify these concepts. For example – what are the **facts** (*known-knowns*), what **questions** (*known-unknowns*) do we have, what do we know will work but don’t know why (**intuition**, or *unknown-knowns*) and where might we **explore** next (*unknown-unknowns*). These can be helpful triggers to build into knowledge management practices to uncover important knowledge – in particular tacit knowledge – on which to make decisions and direct future efforts to acquire new knowledge and in turn reduce risk. The researcher expects this thought model would also be of significant benefit to the process of quality risk management.

<i>Knowns</i>	1. Known Knowns Things we are aware of and understand. <i>Facts</i>	3. Known Unknowns Things we are aware of but don’t understand. <i>Questions</i>
	2. Unknown Knowns Things we understand but are not aware of. <i>Intuition</i>	4. Unknown Unknowns Things we are neither aware of nor understand. <i>Exploration</i>
<i>Unknowns</i>	<i>Knowns</i>	<i>Unknowns</i>

Figure 2-19 – Knowns and Unknowns

2.5 Literature review summary

This literature review has covered diverse territory – regulatory guidance, industry guidance, academic research, risk and knowledge management concepts, technology transfer literature, knowledge transfer literature, and the arguably abstract world of ‘unknown-unknowns.’ Key points relative to each section have been summarised at the close of each section. In aggregate this literature review helps confirm the problem pursued by this research study, along with its complexity, and also provides substrate to refer back to during framework development to help test the outputs from this study.

The next chapter will present the research design, methodology, and methods applied for this study, and share various perspectives of the researcher.

Chapter 3: Research Design, Methodology, and Methods

The purpose of this chapter is to outline the research design, methodology, and methods. This includes the researcher's worldview and insider perspective, the research questions and associated methodology and methods applied, the research timeline and ethics and privacy considerations.

3.1 The researcher's worldview

It is necessary for any researcher to be conscious of how they view the world, notice and process stimuli, formulate positions, communicate such positions, and employ a variety of other processes. Otherwise, the researcher would risk being blind to their assumptions and biases. There are entire fields of study for such philosophical concepts, including definitions of *ontologies* and *epistemologies*. *Ontology* involves the study of 'being' and is concerned with 'what is,' including the nature of existence and structure of reality (Crotty, 1998). *Epistemology* involves a way of looking at the relationship between the knower and the known (Guba and Lincoln, 1994) and how we know what we know (Crotty, 1998).

This researcher's *ontological* belief is that reality is what works and is what is most useful and practical. The researcher's *epistemological* belief is that reality is known through using many tools of research that reflect both objective and subjective evidence (Creswell and Poth, 2017).

A *worldview* is defined by Guba as 'a basic set of beliefs that guide action' (Guba, 1990). Creswell uses the term worldview to describe four general philosophical orientations about the world and the nature of research that a researcher brings to a study (Creswell and Creswell, 2020). These are widely discussed in the literature and shown below in Table 3-1.

Table 3-1 – Four worldviews (Creswell and Creswell, 2020)

Postpositivism	Constructivism
• Determination	• Understanding

Postpositivism	Constructivism
<ul style="list-style-type: none"> • Reductionism • Empirical observation and measurement • Theory verification 	<ul style="list-style-type: none"> • Multiple participant meanings • Social and historical construction • Theory generation
Transformative	Pragmatism
<ul style="list-style-type: none"> • Political • Power and justice oriented • Collaborative • Change-oriented 	<ul style="list-style-type: none"> • Consequences of actions • Problem-centred • Pluralistic • Real-world practice oriented

The researcher most closely associates with the worldview of *pragmatism*, with a problem-centred, real-world practice-oriented study. This worldview is reinforced throughout this thesis, including the desire to deliver meaningful and useful outcomes as a result of this research study. The researcher has a bias toward ‘fit-for-purpose’ and practical approaches to understand and solve problems, based on the researcher’s experience with lean six sigma¹⁸ and a variety of other management sciences¹⁹ as a means to improve operational performance.

Furthermore, the research topic is positioned well in the worldview of pragmatism, given the relative immaturity in awareness and practice of KM in the pharmaceutical industry as explored in Chapter 2. A purely theoretical view of KM can likely be conceptually modelled, perhaps even using fluid dynamics principles as carried out by Smith (Smith, 2005). However, it is the researcher’s belief that if KM cannot be seen as tangible, actionable, of value, and able to deliver benefits to patients and businesses alike in the real world, the practice risks being seen as a ‘management fad and fashion.’ In fact, some have already attacked KM as being too utopian of an idea (Wilson, 2002). Thus, the research study aimed to solve the problem of the lack of KM adoption in the real work of pharmaceutical manufacturing, taking a pragmatic approach focusing not on the research methods, but on the research problem and developing solutions to address it.

¹⁸ A methodology for improving customer satisfaction and improving business processes through a structured set of techniques and tools to reduce variability and improve performance of processes that are value added and aligned with customer desires. (Six Sigma Daily, 2020)

¹⁹ The use of scientific methods and ideas to understand business and management problems and decisions, or the formal study of management; Management science is concerned with designing and developing new and better models of organisational excellence. (Cambridge, 2020)

Pragmatism is concerned with applications, what works and solutions (Patton, 1990); this is the primary objective of the researcher to move the industry forward by understanding the current state (i.e., as is) and delivering solutions to educate and demonstrate what is possible (i.e., what could be).

Mixed-methods research is particularly well-suited for a pragmatic worldview, as the researcher can adapt the methods to the most appropriate means to characterise the problem and the solution (Creswell and Creswell, 2020). Further detail on these methods is presented in section 3.4 of this chapter.

3.2 The researcher's insider perspective

As stated in Chapter 1 (section 1.3), the researcher is employed in pharmaceutical industry and has been for 20+ years. Prior to his career move to knowledge management, the researcher started his career in pharmaceutical manufacturing, in a site-based science and technology role, on the receiving end of technology transfers supporting process demonstrations of small molecule APIs. In this role, the researcher gained experience as a stakeholder of technology transfer. The researcher has also spent nearly a decade in a global engineering role starting up new GMP manufacturing facilities, being responsible for the specification, design, build, and validation of highly complex shop floor automation systems. As such, the researcher was part of several technology transfers, working to automate the manufacturing of the product and processes being transferred, typically new product introductions from research and development. During this time, the researcher also gained deep experience with computer system validation, including the concepts of configuration management, which included robust processes for tracking documents and other critical information associated with the state of a GMP control system. Unbeknownst to the researcher at the time, these practices were a form of knowledge management and perhaps a prelude to the researcher's knowledge management career.

Given the researcher's employment in the industry, experience with technology transfer, and decade of experience in knowledge management, the researcher acknowledges having an *insider perspective* and undertaking *insider research*. The term 'insider research' is used to describe research projects where the researcher has a direct involvement or connection with the research setting (Robson, 1993), cited by (Rooney, 2005). The idea behind the 'insider perspective' is that it can be seen as having both 'pros and cons' (i.e., advantages and disadvantages) as categorised by Greene (Greene, 2014). A synopsis by the researcher of each category based on Greene's description is as follows:

- **Pros (advantages):**
 - **Knowledge:** Insider researchers often do not have to worry about orienting themselves with the research environment and/or participants; they can ask more meaningful questions and better understand the history and practicality of the research topic.
 - **Interaction:** Insider researchers are more familiar with the group under study, know how to approach individuals, and are more likely to engage in discussing issues.
 - **Access:** Insider researchers will know how to gain access and may have existing contacts within the group under study.

- **Cons (disadvantages):**
 - **Too subjective:** Insider researchers risk having narrow perceptions due to familiarity and normalisation with the group under study, thus impacting the ability of the researcher to be objective. In addition, there is increased risk of assumptions based on prior knowledge and/or experience.
 - **Biased:** Insider researchers risk bias as the researcher may be considered too close to the group under study. This bias may influence study methodology, design, and/or results. Insider researchers must not fear bias, but must be aware of the potential for bias and take steps to mitigate it.

With this awareness, the researcher sought to fully capitalise on the advantages and work to mitigate the risks inherent in the disadvantages. There are several advantages for this research study based on the researcher's knowledge, past interaction, and access, including:

- Knowledge of past KM research
- A network of practitioners in the sector, inclusive of industry, academia, regulators, and several industry organisations (e.g., ISPE, PDA, et al.)
- Experience with application of KM both within and beyond the pharmaceutical industry
- Familiarity on related topics, including risk management, technology transfer and data analytics

Specific to the risks associated with the disadvantages (i.e., subjectivity and bias), the researcher worked to mitigate these risks through:

- Using a mixed methods approach (see section 3.4), where multiple sources of both qualitative and quantitative data were considered where possible
- Balance in these research methods, which included leveraging insights from multiple cohorts of stakeholders (i.e., academia, regulatory and industry) during diverse interactions such as philosophical dialogues, interviews, focus groups and surveys
- Awareness of the risk of ‘group think’ and as such, partnered on research activities with people outside of the researcher’s normal ‘circle’
- Publishing and presenting through a variety of channels and venues, including articles subject to peer review by different editorial boards, to promote further objectivity and limit bias

While a member of industry for many years now, the researcher also recognised the value of stepping outside of the industry view and adopting an academic persona as a part of this research study. This allowed the researcher to bring objectivity, enhancing the connection and access to both academia and regulators through philosophical dialogue, interviews, and other research interactions. By this means, this research study helped bridge the triad of industry, regulatory, and academia perspectives in delivering its results by balancing the theory, practice, and application of regulation.

Finally, although the researcher was employed by a major pharmaceutical company at the time of this research study, this study was undertaken as a matter of personal interest and passion for the research topic, independent of the researcher’s employer. Therefore, the researcher’s perspectives, methods, and results were **not** influenced by

their employer nor did they hold any commitment back to the employer as a sponsor of this research.

3.3 The research questions

The original research proposal, titled *An exploration of end-to-end product knowledge in the pharmaceutical industry*, was submitted to the Technological University Dublin (then Dublin Institute of Technology)²⁰ College of Sciences and Health, School of Chemical and Pharmaceutical Sciences in September 2018 and accepted in October 2018. The research proposal presented at the time was based on the following two hypotheses²¹:

1. *KM adoption in the pharmaceutical industry (henceforth ‘industry’) has been slow as described by Kane in 2018 (Kane, 2018). The first hypothesis of this study is that the industry does not have a holistic, end to end view of what it knows about its products across the product lifecycle, nor how to best ensure this knowledge ‘flows’ to ensure the best possible product outcomes. These outcomes include product realisation through a readily available, cost effective and high-quality product to patients, as well as additional business outcomes of operational efficiency and a workforce that has the knowledge it needs to do its best work.*
2. *A second hypothesis is, as identified by Kane (Kane, 2018), tacit (e.g., experiential) knowledge is an afterthought during product development and not recognised as a critical knowledge asset. The industry lacks recognition of the importance of tacit knowledge nor has it a means to best capture and access this knowledge across the product lifecycle in particular key activities such as technology transfer.*

Concepts and associated queries were derived from these hypotheses based on preliminary observations from the research during literature review, initial engagement of the public during early presentations about the research study, and from philosophical dialogues with TU Dublin PRST members. Concepts 1 and 2 were nascent at the start of the research, based on the recent research outputs of Kane (Kane, 2018), as follows:

²⁰ The researcher was a student at Dublin Institute of Technology, which merged with two other Irish institutions to become Technological University Dublin in January 2019.

²¹ These hypotheses statements were adapted during the course of the study for improved clarity as presented in Chapter 1, section 1.4.

Concept 1: Knowledge and management thereof are critical to the realisation of an effective PQS, and knowledge management has been positioned as an enabler to the PQS, yet there is a lack of guidance for what knowledge should be managed or how organisations might go about this.

Associated Queries:

- Are knowledge and knowledge management important to the PQS? Why?
- Is there guidance on knowledge management for the industry, including for knowledge-intensive processes such as technology transfer?
- Is knowledge transfer effective during technology transfer?

Concept 2: The importance of tacit knowledge is under-recognised, and the industry lacks the means to effectively recognise, manage and transfer tacit knowledge, putting it at risk of being under-utilised or lost. Incomplete tacit knowledge transfer can have long term impacts on product manufacturability.

Associated Queries:

- Is tacit knowledge important to the PQS?
- How does one 'recognise, manage and transfer' tacit knowledge?
- What are the benefits to improving tacit knowledge transfer?

During the course of this research study with the realisation of the lack of connectivity between QRM and KM as described in Chapter 1, a third hypothesis emerged and influenced the direction and focus of the research study. This hypothesis is as follows:

3. **Quality risk management and knowledge management are not adequately integrated to ensure the best possible risk-based decisions.** Strengthening this relationship between QRM and KM has the opportunity to improve patient-focused outcomes across the product lifecycle through reduced risk to product quality and availability.

Concepts and associated queries derived from the third hypothesis are as follows:

Concept 3: Knowledge and risk are inherently inter-related, yet this relationship is not well recognised. As such, the industry has not maximised the opportunity to apply thoughtful knowledge management to ensure the best possible risk-based decisions from quality risk management, nor for quality risk management, to inform knowledge management.

Associated Queries:

- What is the relationship between knowledge and risk?
- What is the relationship between knowledge management and risk management?
- What is the benefit to patients of better understanding and exploiting the relationship between knowledge management and quality risk management?

Two distinct research questions evolved from the three hypotheses during the course of the research, given as follows:

1. Research question 1 (RQ1): How can the interdependency between knowledge management and quality risk management be clearly described in a manner that links the two PQS co-enablers to deliver the best possible risk-based decisions?
2. Research question 2 (RQ2): How can technology transfer benefit from a robust and standardised approach to knowledge management to ensure the effective transfer of both explicit and tacit knowledge, leading to improved realisation of the goals of the PQS?

3.4 Research study design, methodology, and methods

The researcher, based on his ontological and epistemological stances and resulting worldview, selected a *mixed methods* approach for this study. Specifically, a *mixed methods experimental (intervention) design* was selected for both research questions, given the desire to develop pragmatic solutions that could be immediately evaluated through an actual or simulated intervention (e.g., application of a framework). The concept of a *mixed methods experimental (intervention) design* as illustrated by Creswell is depicted in Figure 3-1 (Creswell and Creswell, 2020).

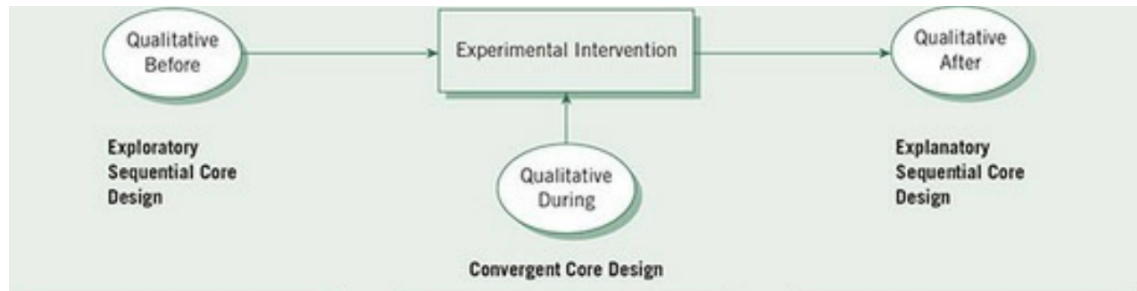


Figure 3-1 – Mixed methods experimental (intervention) design as illustrated by Creswell (Creswell and Creswell, 2020)

From Figure 3-1, it can be seen that experimental intervention can include exploratory, sequential, convergent, and explanatory sequential designs.

The design for this research followed a similar concept to Figure 3-1 and utilised both qualitative and quantitative methods with exploratory sequential, convergent, and explanatory sequential core designs in series [(QUAL → Quan) + QUAL + (QUAN → Qual)]²². This design was selected to establish a baseline understanding prior to the intervention (i.e., exploratory), assess the effectiveness of the intervention (to inform refinement of the intervention), and follow the intervention with an explanatory phase.

Figure 3-2, developed by the researcher, illustrates the methodology with supporting rationale and research methods (RM-1a through RM-1e) for research question 1 (RQ1).

²² Notations used to designate mixed methods research design; capitalisation indicates emphasis over lowercase, “+” indicates convergent design, “→” indicates sequential design, “[...]” indicates a series (Creswell and Creswell, 2020)

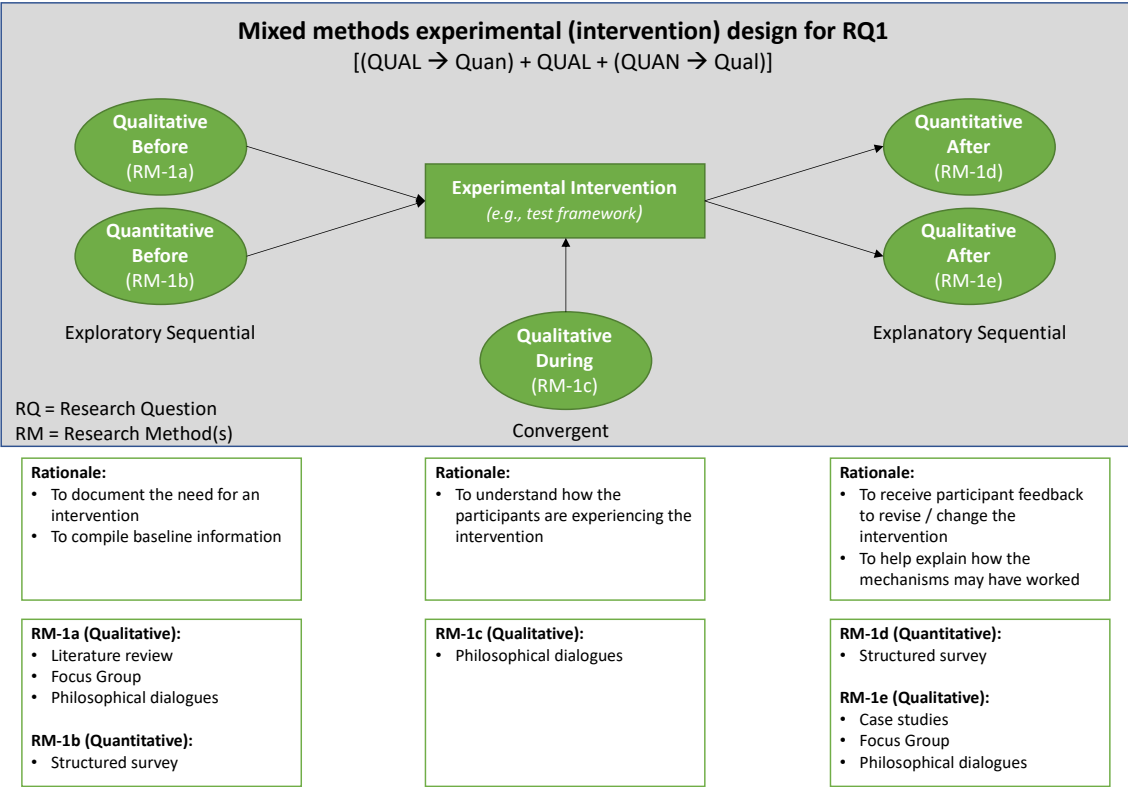


Figure 3-2 – Research Methodology and Methods for Research Question 1

For research question 2 (RQ2), the same overall methodology was used (i.e., *mixed methods experimental (intervention) design*), with minor variations to the research methods applied (RM-2a through RM-2e) as appropriate for RQ2. This is illustrated in Figure 3-3.

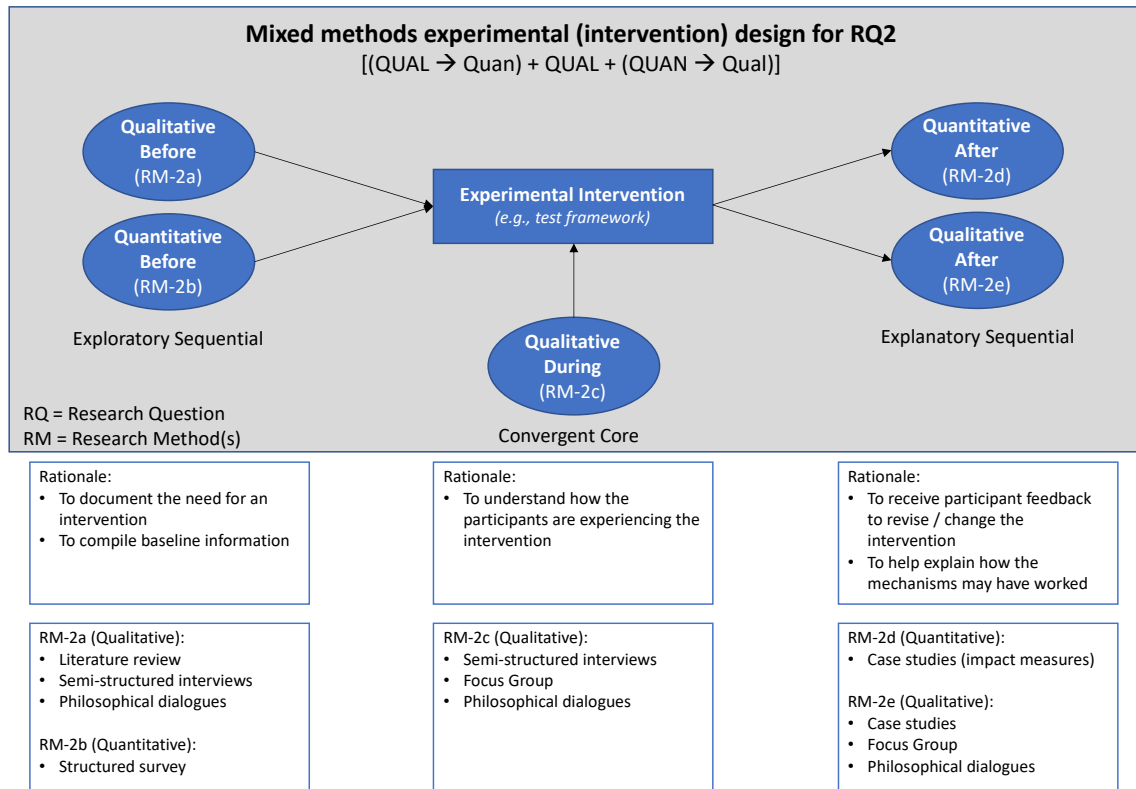


Figure 3-3 – Research Methodology and Methods for Research Question 2

Once the initial research methodology was identified, the researcher applied for ethics approval from the TU Dublin Research Ethics & Integrity Committee, as is discussed in the next section.

3.5 Ethics and privacy

The initial research plan was submitted to Technological University Dublin (at the time Dublin Institute of Technology) on 21-Nov-2018 and received approval from the Research Ethics & Integrity Committee on 28-Jan-2019. All research activities were conducted in accordance with TU Dublin’s Ethical Guidelines (TU Dublin, no date). Specifically, the researcher:

- Sought formal consent from interview participants prior to any research activity being undertaken. Formalised consent forms were provided to the interviewees, along with information packets in advance of interviews. The interviews did not proceed without consent granted.
- Handled and stored personal information in a strictly confidential manner, in a secure and password protected location, using TU Dublin IT systems.

- Used data gained during this research study solely for the purpose of this research study.
- Did not (and will not) have any power over any of the involved research subjects, each of whom agreed voluntarily to participate.

The researcher also undertook formal Research Integrity Training sponsored by TU Dublin and received competency-based certificates for the domains of *Engineering and Technology* and *Social and Behavioural Sciences*. These modules train researchers on their professional responsibilities and on how to deal with complex issues that can arise while planning, conducting, and reporting research.

Part Two of this thesis follows (including Chapters 4 through 7) and presents many of the research activities and corresponding outputs, including a process model for KM, a framework to integrate knowledge and risk, and a framework to enhance knowledge transfer during technology transfer.

Part Two: Advancing KM and Developing QRM-KM Connectivity

Part Two explores the relationship between knowledge and risk and the opportunity to better integrate knowledge management and quality risk management. In response to findings of this exploration, potential solutions are provided through a newly proposed model and multiple frameworks.

- Definition of a Process Model for Knowledge Management (Chapter 4)
- Re-imagining the QRM-KM interdependency with a novel framework to connect QRM and KM (Chapter 5)
- A definition of requirements to improve knowledge transfer during technology transfer (Chapter 6) and associated framework and toolkit to enhance knowledge transfer effectiveness (Chapter 7)

Chapter 4: A Process Model for Knowledge Management

Anticipating the opportunity for KM to be better integrated with QRM, the purpose of this chapter is to propose a *Knowledge Management Process Model* as a means to advance the understanding of the ‘how’ behind high level KM concepts.

Not only is the integration between QRM and KM severely lacking in practice today (Lipa, O’Donnell and Greene, 2021) but also the level of adoption and maturity of KM in the pharmaceutical industry is far behind that of QRM as presented in Chapter 1. While many factors highlighted in Chapter 1 are well out of the control of the researcher (e.g., the existing body of literature for QRM vs. KM), there was one concept identified where the researcher could work to influence immediately: **The understanding of what knowledge management is**. The following section describing a process model for knowledge management is a summary of a peer-reviewed paper by the researcher published in the *Journal of Validation Technology* (Lipa, O’Donnell and Greene, 2020a).

4.1 Introducing a Knowledge Management Process Model

The practice of KM presents a diverse and adaptive set of practices to enhance knowledge flow and application. A well-designed, holistic, and systematic KM program will strengthen QRM through the availability of critical knowledge, including product knowledge, process knowledge, platform knowledge, and other relevant knowledge. Such a KM program can support the curation, sharing, and dissemination of knowledge which can subsequently be transferred and applied to inform decisions and achieve other objectives.

Typically, this knowledge resides in documents housed in repositories or can be found within communities, lessons learned, best practices, experiences, and expertise. This can also include knowledge from other products, other sites, or other modalities, as well as knowledge from past changes, from prior risk assessments, and a wide variety of other sources.

The researcher had long recognised that it was challenging to concisely explain the ‘how’ behind KM, often using the analogy that ‘knowledge management is about getting knowledge to flow.’ But what is the ‘double-click’ on this flow concept? Upon reflection of this question – on how best to explain KM and how to do so in a manner familiar to the pharmaceutical sector – the researcher decided to attempt to do so by *using the quality risk management process diagram as the basis.*

The ICH Q9 QRM process model (ICH, 2005) is depicted in Figure 4-1 and provides an informative visualisation of the process of risk management. Included in the process model is a depiction of the key steps and sub-steps within a risk management process, the sequence of steps including relationships between steps and feedback loops, and supportive or enabling elements to the core process (e.g., *Risk Management tools*).

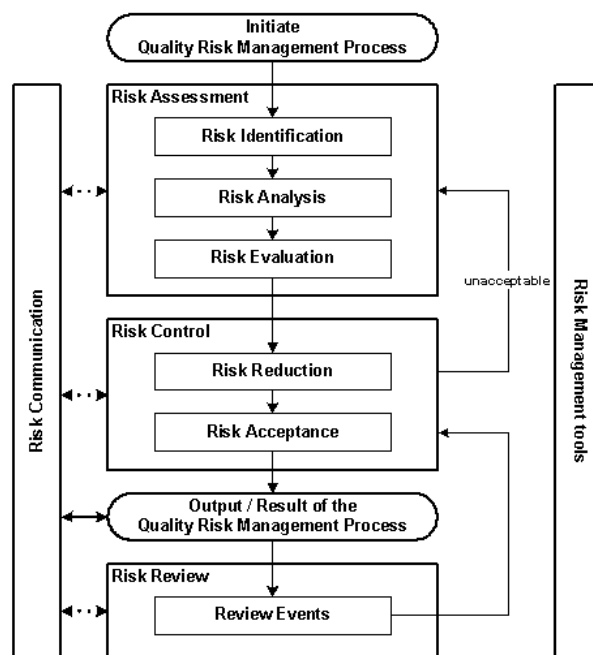
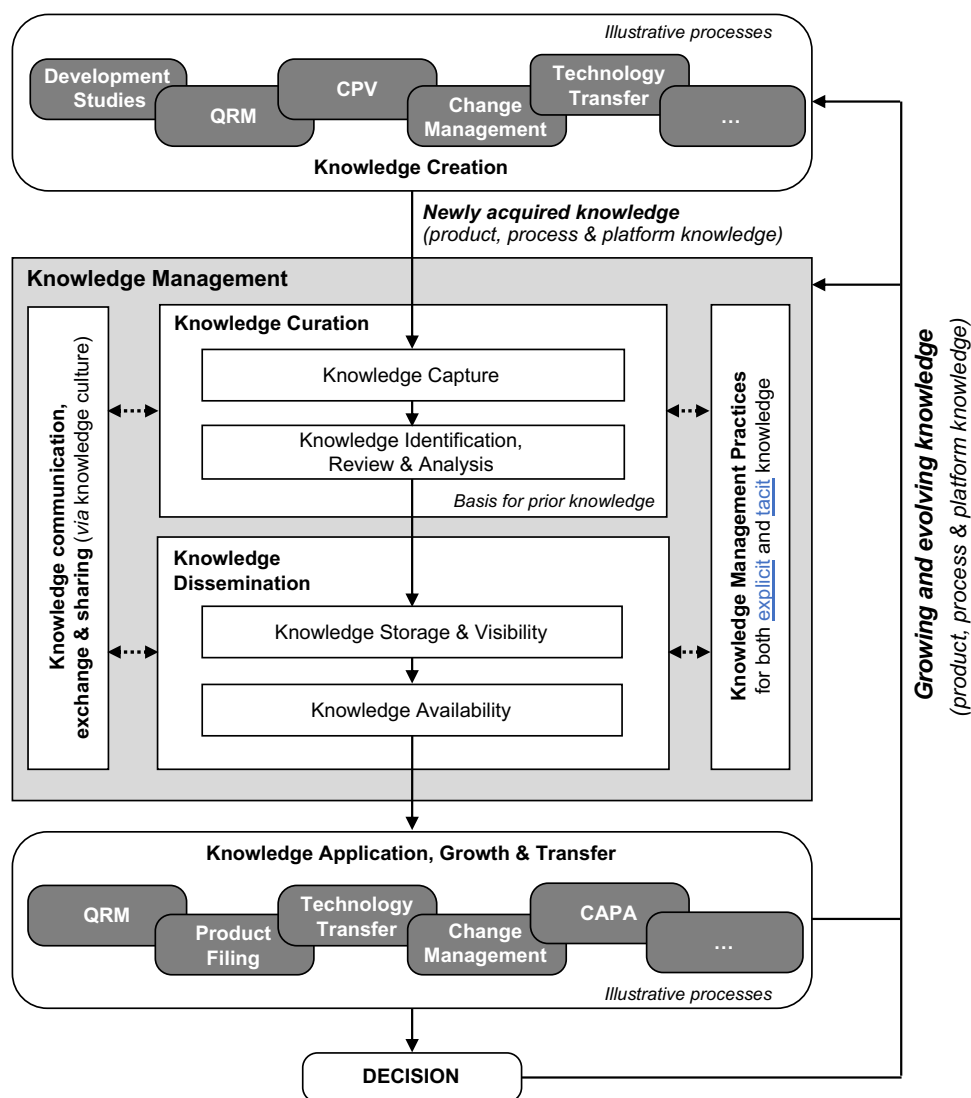


Figure 4-1 – ICH Q9 QRM process model (ICH, 2005)

Starting with the ICH Q9 QRM process model as a framework and then applying common definitions of KM included in Chapter 2 (section 2.1), drawing upon multiple philosophical dialogs with thought leaders in QRM and KM, and over 10 years of professional experience, the researcher through multiple iterations created a *Knowledge Management Process Model* as depicted in Figure 4-2.



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Figure 4-2 – Knowledge Management Process Model

This new *Knowledge Management Process Model* features traceability to the definition of KM in ICH Q10 (i.e., ‘systematic approach to *acquiring, analysing, storing, and disseminating* information...’) (ICH, 2008). Each of these activities defined in ICH Q10 are represented in the model. In the opinion of the researcher, this process model further significantly enhances the ICH Q10 definition through additional context, details, and mapping of interactions within the model. Similar to the QRM process model, this model includes a depiction of the key steps and sub-steps within a KM process, the sequence of steps including relationships between steps and feedback loops, and supportive or enabling elements to the core process (e.g., *Knowledge Management Practices*).

The following are highlights of the model:

1. Knowledge is **acquired (created) through a variety of important processes and activities**. This knowledge must flow into the knowledge management construct to be ‘managed’ (i.e., to be systematically curated, shared, and disseminated for future use).
2. The overall process of knowledge management is divided into two main activities. A phase for **knowledge curation**, where knowledge is intentionally *captured* and subsequently *identified, reviewed, and analysed* as appropriate. Curation²³ is defined as ‘the action or process of selecting, organising, and looking after the items in a collection’. This activity involves proactively stewarding and caring for the knowledge assets of the organisation to ensure they are available and suitable for use when needed. The second phase is **knowledge dissemination**, where the importance of not only knowledge *storage* but also *visibility* and *availability* (inclusive of accessibility) are highlighted. Of note, *knowledge dissemination* may be on a ‘pull’ and/or a ‘push’ basis, meaning it can be ‘pulled’ on demand by a process (e.g., obtain specifications for technology transfer) or it can be ‘pushed’ to those that need to know (e.g., sharing a lesson via a community or by building into a business process).
3. The ‘how’ for these two major activities is accomplished through **KM practices**²⁴. Practices should be employed for both explicit knowledge (e.g., content management, taxonomies, search) and tacit knowledge (e.g., communities of practice, expertise location, lessons learned). These KM practices are best supported by a series of enablers (e.g., standardised processes, sponsorship, and training) (Kane and Lipa, 2018).
4. **Knowledge communication, exchange, and sharing** represents the sharing of knowledge and learning based on the mindsets and behaviours of an effective knowledge culture (Kane and Lipa, 2018), where people can ask questions, learn

²³ <https://www.lexico.com/en/definition/curation>

²⁴ KM practices, also referred to as KM approaches, capabilities, methods and tools, are the standard and repeatable means by which knowledge is managed. These are akin to the QRM practices, such as the “Risk Management Methods and Tools” found in Annex 1 of ICH Q9 (ICH, 2005)

from each other, and make connections to learn and grow their individual knowledge and collectively that of the organisation.

5. **Knowledge is applied** to a variety of important processes and activities. Knowledge is an indispensable asset which powers a variety of critical processes and enables the **best possible DECISION** (or other desired process outcome) for QRM and many other processes.
6. A **feedback loop** is included for the growth and evolution of knowledge which provides an input to future processes and also grows the knowledge base of the organisation.

To illustrate the similarity to the ICH Q9 QRM process model (ICH, 2005), Figure 4-3 provides a side-by-side comparison of the two process models.

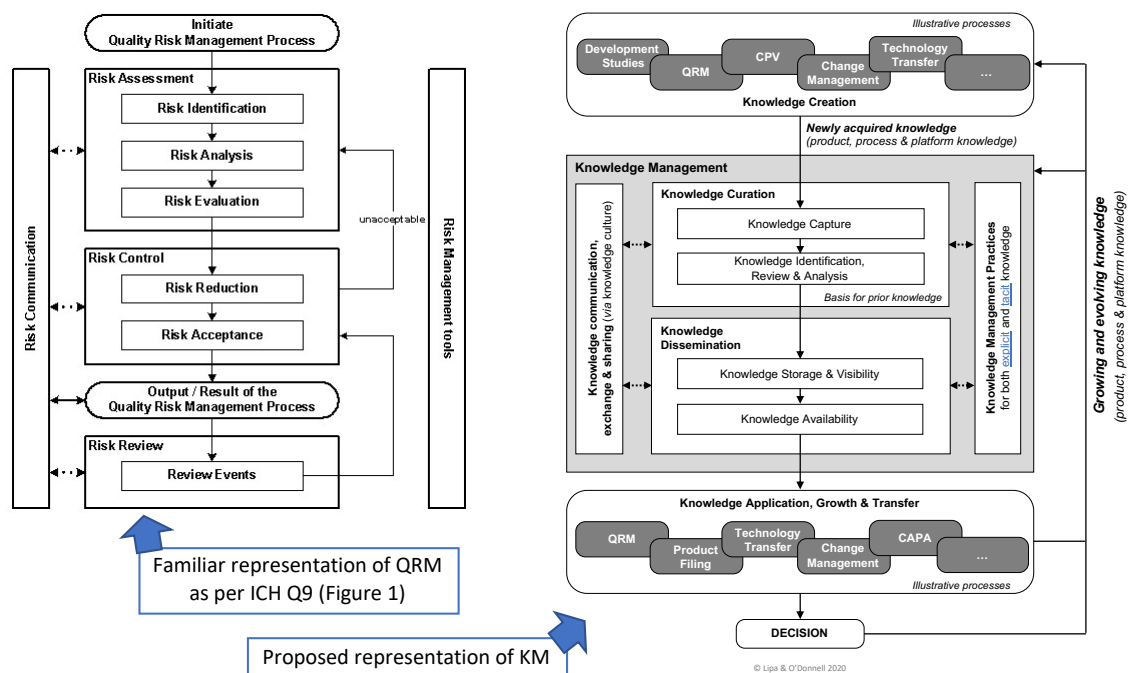


Figure 4-3 – KM Process Model as an analogue to QRM process model

This new process model was reviewed as part of the industry SME author team developing the *ISPE Good Practice Guide for Knowledge Management* (ISPE, 2021b), of which the researcher is a member. The industry SME author team ratified use of this *Knowledge Management Process Model* as a central element to the ISPE Guide, featured as its own chapter in the guide. The researcher made a further original

contribution to the *ISPE Good Practice Guide for Knowledge Management* by providing a detailed discussion on each activity in the model. This is presented as Chapter 4 in the ISPE Guide (of which the researcher was the lead author).

One can envision the benefit to improved understanding and decreased uncertainty by 'unlocking' the knowledge of the organisation in the manner described in the *Knowledge Management Process Model*, as well as to many other benefits of knowledge access and availability for resolving investigations, post-approval changes, and more. It is the discipline of KM that makes this a reality. Having aligned KM and QRM as dual enablers, the researcher was curious to further explore their interrelationship. Chapter 5 of this thesis describes this work.

Chapter 5: Re-Imagining the QRM–KM Interdependency

The purpose of this chapter is to investigate the current state of integration between QRM and KM as dual PQS enablers and to introduce a framework to convey a vision for improved integration and the benefits which could arise as a result of this integration. This chapter first builds on a detailed literature review conducted by the researcher (Lipa, O'Donnell and Greene, 2020c) and published in a peer-reviewed journal, the *Journal of Validation Technology*. Subsequently, the development of the framework to connect risk and knowledge is described in detail in a peer-reviewed paper by the researcher (Lipa, O'Donnell and Greene, 2020a). The following sections of this thesis represent key insights from these papers.

5.1 A look at the connectivity between QRM and KM

Arguably, the most familiar representation of the QRM and KM relationship originates from the ICH Q10 PQS model (ICH, 2008) where the two enablers are positioned adjacent to each other, but notably not connected (Figure 5-1).

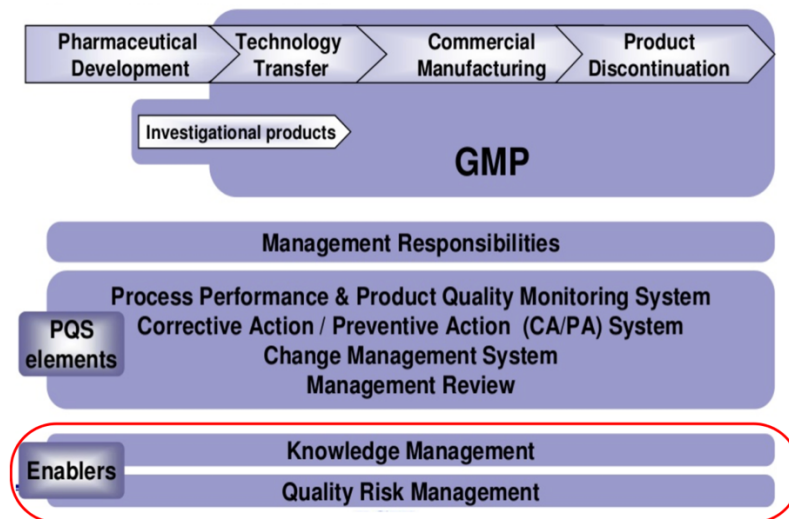


Figure 5-1 – KM and QRM as adjacent yet disconnected enablers of the PQS

Key insights gained during the course of this research from literature review and other inputs on *risk, risk management, knowledge, and knowledge management*, include:

- Risk varies inversely with knowledge, or more accurately risk varies inversely with knowledge *application*, suggesting that knowledge has to be available and actively used in the reduction of risk; given the overarching goal of risk management is to *minimise* risk, this relationship suggests one should maximise knowledge and its application to inform risk
- Knowledge is both an *input* and an *output* to the risk management process which in turn informs risk; essentially, knowledge weaves in and out of the various activities within the risk management process
- Knowledge management is about knowledge flow and ultimately knowledge application
- Quality risk management can enable the best outcomes and further reduce risk to patients by leveraging the best available knowledge about products, processes, and platforms, including prior knowledge
- Quality risk management is a discrete event in applying knowledge to inform decisions (i.e., the basis of risk-based decision making)
- The goal of KM is to deliver the best available knowledge to the right person, at the right time *in order to* make the right decision and/or give the right advice

It would then seem logical that QRM and KM should be thoughtfully connected in some manner to ensure the best knowledge is available and applied to ensure the best possible risk-based decisions are made in support of an effective PQS. In a manner of speaking, *knowledge is the currency of managing risk*.

There is broad agreement on the concept that QRM and KM should be linked in some way as confirmed through a survey by the researcher issued to industry and regulators. The full details of this survey are published in *Level3* (Lipa, O'Donnell and Greene, 2021), and will be discussed in detail when considering the holistic impact of this research study in Chapter 10. But for now, focusing on the question which solicited their opinion of how interdependent QRM and KM are as theoretical concepts, 97% of respondents indicated QRM and KM are highly interdependent (Figure 5-2).

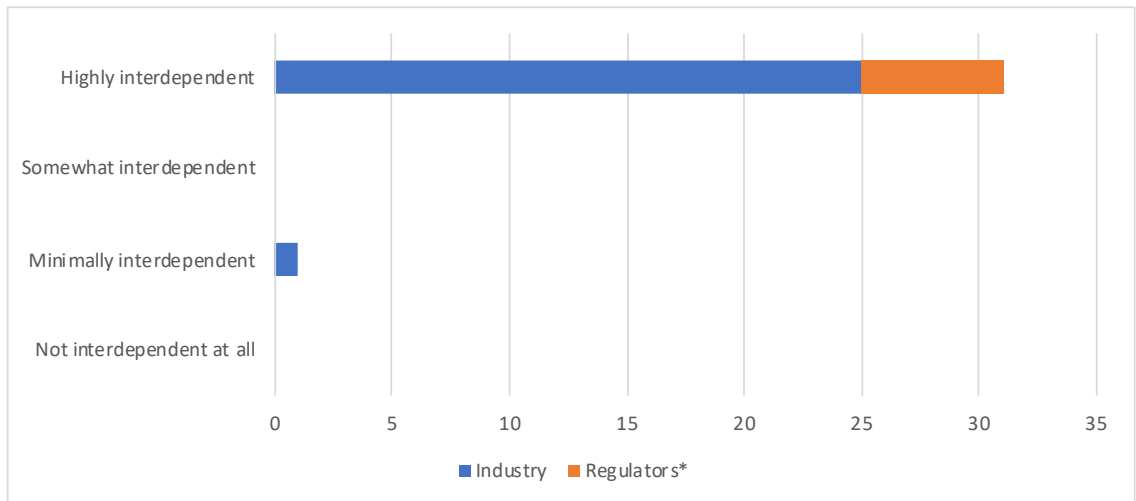


Figure 5-2 – How Interdependent are QRM and KM as theoretical concepts? (Lipa, O’Donnell and Greene, 2021)

However, when asked about how integrated QRM and KM are in practice today, the answer was very different. Eighty-four percent (84%) indicated QRM and KM are only partially integrated in practice and 13% indicated QRM and KM are not integrated at all. Only one respondent (3%) indicated QRM and KM were intentionally integrated (Figure 5-3).

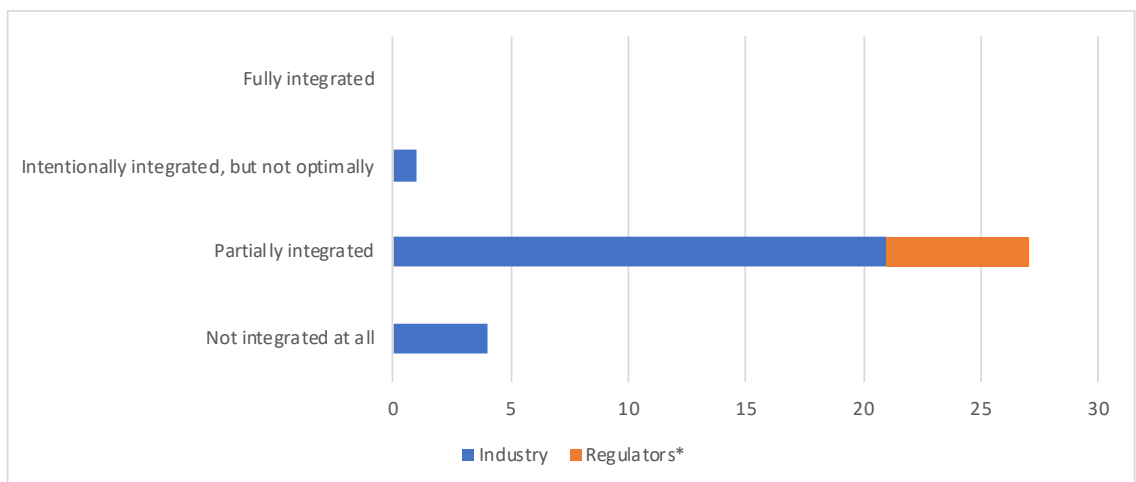


Figure 5-3 – Across the industry and in general terms, how integrated do you think QRM and KM are in practice today? (Lipa, O’Donnell and Greene, 2021)

The reasons for this may not be surprising given the lagging nature of KM adoption in the industry (Chapter 1), suggesting that KM is not adequately understood and/or sufficiently defined and mature.

Furthermore, in the opinion of the researcher, there is a fundamental gap in understanding of the opportunity (and expectation) to exploit the synergy between these two critical disciplines. The discipline of QRM – with good intent – has been focused on how to “do QRM,” and the discipline of KM has similarly been focused on how to “do KM.” Yet there is little evidence QRM has fully engaged with KM (e.g., through the definition of QRM requirements of KM), nor has KM fully embedded itself in QRM as a practice. However, should not the pursuit of the best possible risk-based decisions (and the associated risk reduction to patients) be a sufficiently important reason to address this gap?

5.2 Development of the Risk-Knowledge Infinity Cycle

In response to this important opportunity, the researcher sought to address this gap through better defining the QRM-KM relationship. The researcher believed there is an opportunity for broad impact across many stakeholder groups with an increased appreciation of such a synergistic relationship, including QMS practitioners, KM practitioners, the leadership, and other stakeholders in a firm’s PQS, regulators, and ultimately patients.

Building off of the rudimentary cyclical concept depicted in Figure 1-3, in partnership with a thought leader on QRM²⁵ and after several philosophical dialogues and iterations, the researcher worked to develop a new and novel framework to connect QRM and KM. The researcher desired to convey certain attributes – including connectivity, balance, flow, and duality. The researcher also wanted to convey the continuous, ongoing learning that should happen across a product lifecycle, during which knowledge is routinely growing (even if it is a reaffirmation of what is already known). Finally, the researcher sought to ensure the framework featured a ‘closed-loop’ process²⁶ to reinforce that risk and knowledge are inextricably linked. In response to these inputs,

²⁵ The researcher solicited input from Dr. Kevin O’Donnell who is a recognised thought leader on QRM and is the rapporteur of the current team to revise ICH Q9.

²⁶ “the complete path followed by a signal as it is fed back from the output of a system to the input and then back to the output” (dictionary.com)

the researcher proposed a new framework, the *Risk-Knowledge Infinity Cycle* (or *RKI Cycle*), as presented in Figure 5-4.

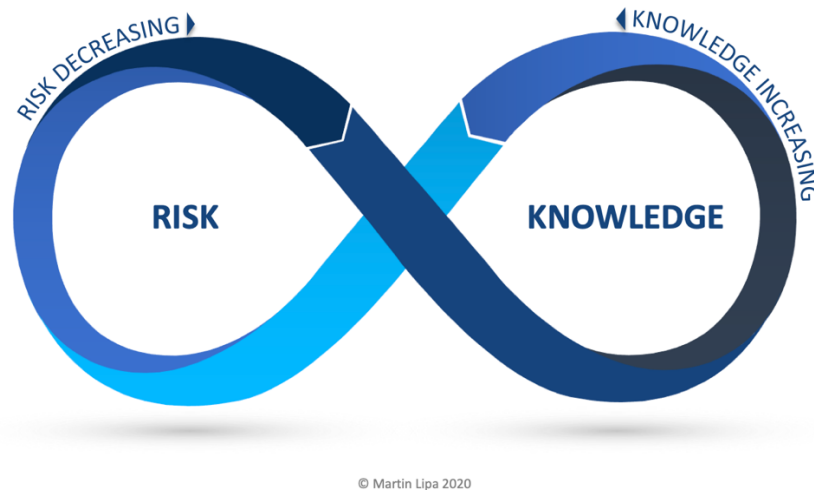


Figure 5-4 – The Risk-Knowledge Infinity Cycle

This framework is intended to enable the visualisation and understanding of the Risk-Knowledge relationship in a new and practical way, supported with descriptive details and an example provided in the referenced peer-reviewed paper (Lipa, O’Donnell and Greene, 2020a). In summary, key features of this framework include:

- (i) the **interwoven relationship** between knowledge and risk, where knowledge feeds in to inform risk and risk informs what is known, including the need to acquire new knowledge: knowledge and risk inform each other.
- (ii) the **inverse relationship** previously established, where increased knowledge leads to decreased risk. Figure 5-5 below provides a visualisation of this concept over time for a product. In the early stages of a product’s lifecycle, risk is *high* since knowledge is *low*. Risk can be immediately reduced through the application of prior knowledge, and risk is further reduced through increasing and applying knowledge by other means, including development activities, manufacturing experience, and risk review. A well-characterised product for which there is an abundance of knowledge will result in lower risk.



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Figure 5-5 – Decreasing risk though increasing applied knowledge over time

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

Turning attention to an example of *RKI Cycle* application focused on the PQS as defined by ICH Q10 (ICH, 2008) can help illustrate the relationship between quality risk management and knowledge management as illustrated in Figure 5-6.

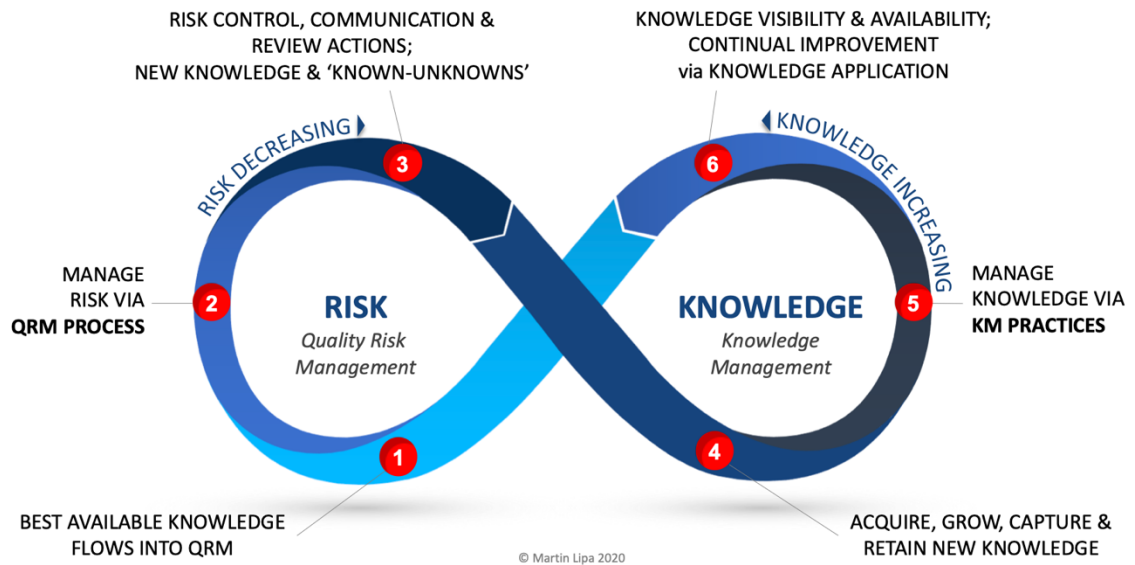


Figure 5-6 – The Risk-Knowledge Infinity Cycle applied to ICH Q10

As illustrated in Figure 5-6, QRM and KM are interdependent and in unison enabling the PQS. The two ICH Q10 co-enablers are not distinct but are in fact interwoven: knowledge informing quality risk, quality risk creating knowledge, knowledge informing quality risk.... This is consistent with research by Lengyel (Lengyel, 2019) who asserts ‘risk management and knowledge management have been shown to exhibit a reciprocal relationship. Risk management identifies knowledge gaps and knowledge management is a means of identifying resources to fill those gaps.’ Observations in applying the *RK/ Cycle* framework to ICH Q10 include the following:

- (i) The recognition of QRM (node 2) and KM (node 5) being separate, distinct disciplines in support of the PQS yet interdependent on each other for ultimately reducing risk to patients.
- (ii) This cycle can repeat for each phase of the QRM cycle, including when new knowledge is acquired, and with each pass through the cycle, knowledge is increased while risk is decreased.
- (iii) Consistent with the underlying framework, the interwoven relationship between knowledge and risk (and knowledge management and risk management), the inverse relationship of increasing knowledge leading to decreased risk, the concept of flow, and the continuous and perpetual cycle are each relevant to the goals of the PQS.

Further details on the *RKI Cycle*, a description of each of the six nodes in the cycle and an example of the cycle for a Sterile Filling Line risk assessment are available in the referenced paper (Lipa, O'Donnell and Greene, 2020a).

Upon socialisation of this framework within the sector via the survey discussed earlier in this chapter (Lipa, O'Donnell and Greene, 2021), preliminary feedback has been overwhelmingly positive. When asked whether this framework is helpful in visualising the relationship between risk and knowledge, 84% responded 'yes' as illustrated in Figure 5-7.

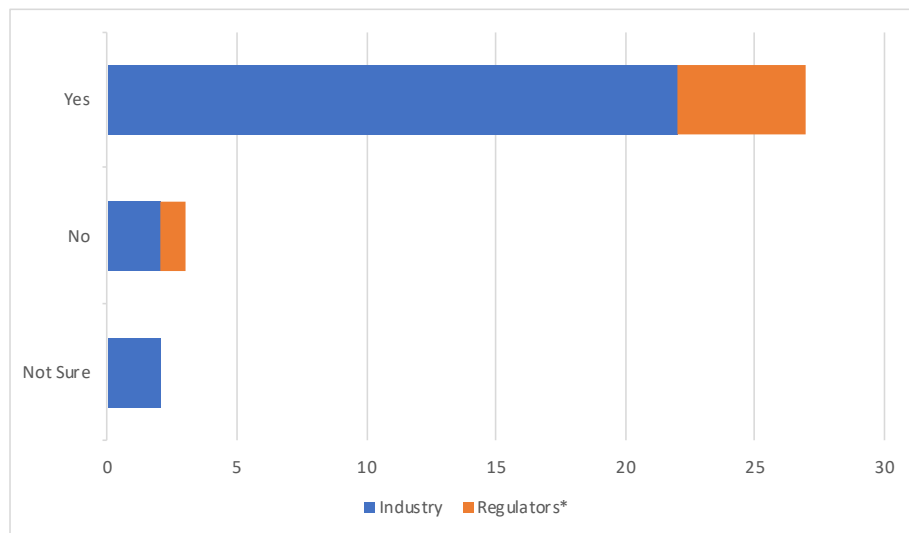


Figure 5-7 – Do you find this framework helpful in visualising the relationship between risk and knowledge

Additional feedback to this framework will be discussed, along with anticipated benefits, in Chapter 10.

Linking back to the origin of this chapter where QRM and KM are represented as distinct enablers, the researcher proposed that the PQS could be better represented with QRM and KM as the basis for a united PQS foundation, and also directly linked to the PQS elements which they enable as represented in Figure 5-8.

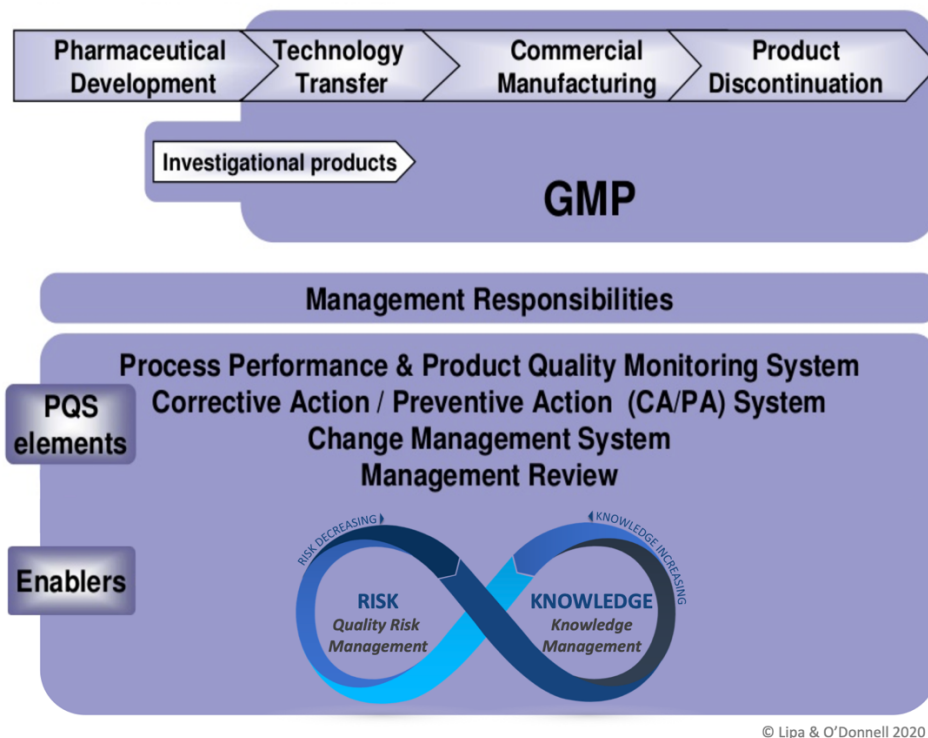


Figure 5-8 – A re-framed and united PQS foundation

Having first established a *Knowledge Management Process Model* as a means to improve understanding of KM (Figure 4-2) and now having further established the *RKI Cycle* framework to address the important disconnect between QRM and KM, the researcher was ready to shift focus to improve KM for the product lifecycle. The researcher selected the lifecycle stage of *technology transfer*, given the challenges typically associated with technology transfer as reported by Kane (Kane, 2018), highlighted during the literature review, and witnessed by the researcher in his professional experience. Furthermore, not only does technology transfer have a direct impact on the ability to achieve the goals of the PQS, but industry trends suggest that the frequency and complexity of technology transfers is expected to increase (McKinsey & Company, 2019a, 2019b; O’Halloran, Heavey and Ciccarelli, 2019), making technology transfer a key area to drive improvement. The following chapter will explore this opportunity in further detail.

Chapter 6: The Opportunity to Improve Knowledge Transfer During Technology Transfer

The purpose of this chapter is to characterise the current state of KT during technology transfer and define requirements for a future framework to address as a means to improve KT.

6.1 Current state of knowledge transfer during pharmaceutical technology transfer

To understand the current state of KT during a pharmaceutical technology transfer, a series of research activities were undertaken, including a literature review (see Chapter 2, section 2.3), a survey, and interviews with industry experts and regulatory authorities. This work has been published in a peer-reviewed paper in the *Journal of Validation Technology* (Lipa, Kane and Greene, 2019). This section presents a summary of this peer-reviewed paper which notably received external recognition in the form of the *2020 Author of the Year Award* by the *Journal of Validation Technology* (IVT Network, 2020).

6.1.1 Survey on knowledge transfer during technology transfer

The researcher, as a presenter at the seminar, *An Audience with Regulatory, Academia, and Industry, on The Role of Effective QRM & KM in Product Realisation for Patients in the 21st Century* on 04-April-2019 at Technological University Dublin conducted an audience survey. The presentation and survey results are presented in detail as part of a published monograph (Lipa and Kane, 2019) and summarised below. The survey was designed to assess the audience perspectives on each the *importance* and *effectiveness* of KT to enable an effective and efficient technology transfer. The survey forms were filled out by hand in session and no identifying information was collected. Fifty-six (56) responses were received.

While several insights can be derived from the survey, the primary finding is depicted in Figure 6-1 evaluating the importance versus the effectiveness for each explicit KT and tacit KT.

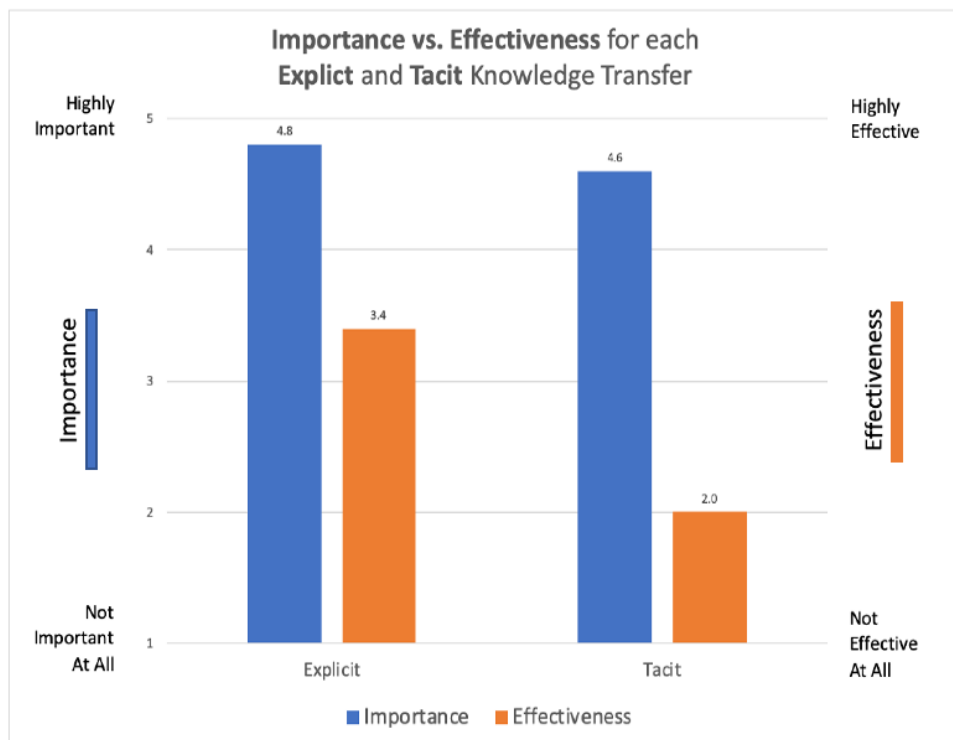


Figure 6-1 – Importance vs. effectiveness for explicit and tacit knowledge transfer

In summary, while explicit and tacit knowledge are each considered *highly important* to effective and efficient technology transfer (axis y1 (blue)), explicit KT effectiveness is only *marginally effective* with notable room for improvement (axis y2 (orange)). Furthermore, tacit KT is regarded as *somewhat ineffective*.

6.1.2 Expert interviews: international industry experts and regulatory authorities

Four experts were interviewed in mid-2019 to explore their perspectives on the importance of KT as a part of technology transfer, on the effectiveness of each explicit and tacit KT, and expectations for tacit KT. The experts were selected in a matrix fashion where two were based in the EU and two based in the USA, and two were industry SMEs and two represented regulatory authorities. An analysis is included in the associated paper (Lipa, Kane and Greene, 2019).

Upon analysis of the interview transcripts, the following key themes emerged:

1. Knowledge transfer could be improved and would have meaningful positive impact to technology transfer outcomes, including cost, quality and product availability.
2. Some companies appeared to do well but this is the exception, not the norm.
3. Transparency on the level of process understanding was critical to a productive regulatory dialog.
4. Often knowledge gets 'stuck' (e.g., someone's judgement it is not important, buried in long documents, captured in an unusable format).
5. On average, knowledge transfer effectiveness of explicit knowledge was marginal and there is wide variation.
6. On average, knowledge transfer effectiveness of tacit knowledge was ineffective to marginal and there is wide variation.
7. Successful technology transfer requires human to human interactions, preferably face to face and time to walk through the details of a process to explore details, sensitivities, what is not known, etc.
8. There was a clear desire that we must get better at technology transfer as an industry.

6.1.3 Current state of technology transfer knowledge transfer

A current state assessment was drawn from three independent research activities (literature review, survey, and expert interviews). The findings across these three distinct activities correlated well and suggested these key observations:

1. Overall, **knowledge transfer is critical to a successful and sustainable technology transfer**. Ineffective knowledge transfer can have a long-lasting impact on the ability of the receiving site to provide cost-effective, high-quality products with the desired availability.
2. **Knowledge to be transferred associated with a technology transfer is biased toward explicit knowledge** (e.g., documents). This explicit knowledge is critical to the success of the transfer, yet the industry is only marginally effective at it – it is clearly not a strength. There is some supporting guidance on explicit knowledge that should be transferred, but not prescriptive means on how to do this or how to measure effectiveness.
3. **Tacit knowledge associated with technology transfer is not widely recognised as an asset to be transferred**, nor is there evidence to suggest the

pharmaceutical industry does it effectively. There is limited understanding on what tacit knowledge is, why it was important, and how it can be transferred, including how to measure effectiveness of the transfer. Furthermore, there is little acknowledgement of tacit knowledge in industry guidance for technology transfer, although there are a few recent developments where tacit knowledge and related concepts (e.g., ‘know-how’) were acknowledged to be important to transfer but without any guidance on how this might happen (Lipa, Kane and Greene, 2019).

4. **Regulators and industry are generally well aligned on these issues and their impact.** Both recognise the opportunity – and the need – to improve KM for the good of patients.

These findings supported the problem statements being explored at the start of this research, namely, that knowledge does not ‘flow’ readily through technology transfer, and that tacit knowledge is critical but is not effectively managed or transferred. The subsequent research activities to develop a KT framework and associated toolkit to improve KT proceeded with the aim to address this opportunity.

6.2 Defining requirements for knowledge transfer during technology transfer

The purpose of this section is to explore the KT challenges associated with technology transfer (i.e., the problem) to gain a clearer understanding of the needs, and from this deeper understanding to identify the requirements a framework for technology transfer KT (i.e., the solution) should address. This section is presented as a summary of a peer-reviewed paper published in the *PDA Journal of Pharmaceutical Science and Technology* (Lipa, Greene and Calnan, 2021).

6.2.1 Common challenges to technology transfer knowledge transfer

There are many potential challenges for effective KT during technology transfer. Each one of these potential challenges presents a failure mode to effective KT and therefore, to sustained technology transfer success. Based on the current state assessment, literature review, interviews with experts (both industry and regulatory authorities), the

experience of the researcher (both in KM and in technology transfer), and various philosophical dialogues, the researcher identified six KT challenges. Figure 6-2 developed by the researcher illustrates these challenges in the context of technology transfer as a stage in the pharmaceutical product lifecycle. A brief description of each challenge follows.

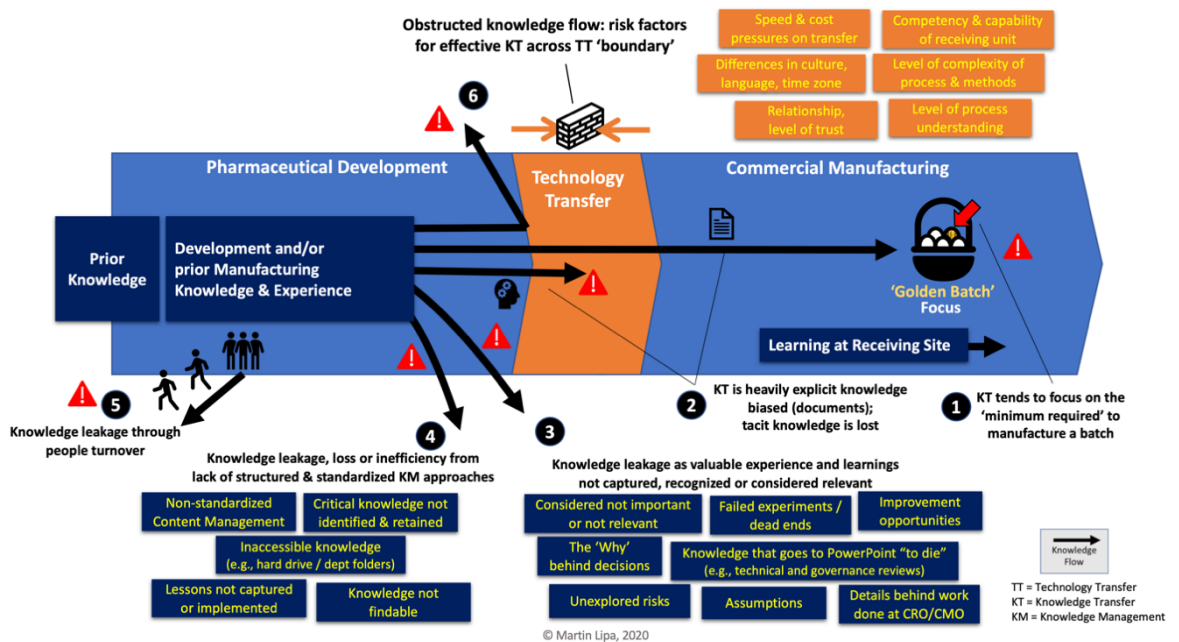


Figure 6-2 – Challenges associated with technology transfer knowledge transfer

Challenge 1: Narrow focus on the ‘golden batch’²⁷ which was often regarded as the ‘minimum required’ by the receiving site to successfully manufacture the product. The focus tended to be on transferring the knowledge required for ‘what goes right.’ Knowledge associated with ‘what goes wrong’ is often not transferred.

Challenge 2: Knowledge transfer was heavily biased toward documents, while tacit knowledge (‘know-how’) was not methodically transferred. KT was typically focused on document transfer (i.e., explicit knowledge). While some tacit KT activities do occur on an ad hoc basis (e.g., staff at the receiving unit witnessed a batch being manufactured at the sending unit), these attempts at tacit KT tended to be unstructured

²⁷ The term ‘golden batch’ has been commonly attributed to batch process automation. The researcher uses this term with some caution not intending this to be the ‘perfect batch trend’ but rather to convey the scenario which progresses to plan without any deviations from the expected outcomes.

and highly variable in approach. Therefore, while explicit knowledge may be transferred to the receiving unit, often valuable tacit knowledge was not transferred and may be lost.

Challenge 3: Knowledge ‘leakage’* occurred when valuable experience and learnings were not captured, recognised, or considered relevant. This included useful knowledge such as failed experiments, the ‘why’ behind decisions, unexplored risks, improvement opportunities (quality, cycle time, yield), other product/process experience known by experts but never written down, and knowledge that is less structured or formal that figuratively ‘went to PowerPoint to die’ (e.g., lessons learned, important decisions in governance reviews, etc.).

**A word about knowledge leakage:* The researcher would like to call out the usage of the concept knowledge ‘leakage’ in these challenges. The researcher naively (and at the time, hoped creatively) labelled these challenges with this concept when trying to describe what was happening in practical terms. Simply – that knowledge was being lost, or dissipating, or ‘leaking’ from the boundaries where it was once known to be (e.g., the project team). Upon a review of the literature, the researcher was surprised to learn knowledge leakage was an established concept, and there are nominally two broad definitions of ‘knowledge leakage’ in existing literature: (i) ‘knowledge and capability shortage. This refers mainly to turnover, i.e., individuals retire, move to another organisation, or leave an organisation due to other reasons. Regardless of the specific form of turnover, those individuals take their tacit knowledge and relational capital with them and it is often the case that there is no one in the organisation experienced and skilled enough to replace them.’ (Durst and Ferenhof, 2014). And (ii) simply, ‘the loss of knowledge intended to stay within a firm’s boundaries’ (Durst, Aggestam and Ferenhof, 2015). This latter definition seems to have received more attention in the literature, due to attention on risk of loss of intellectual property and associated competitive advantage – whether the loss is intentional or not – through partnerships, technology transfers, software development projects or other collaborations. However, the literature also states that the topic of knowledge leakage is not well characterised or understood, and more research is required (Durst, Aggestam and Ferenhof, 2015).

Given this ambiguity about the concept of knowledge leakage the researcher proposes a practical definition of knowledge leakage for the purposes of this thesis with the hope it will garner further study: that **knowledge leakage refers to unintended loss, dissipation, mismanagement, lack of structure or any other mechanism which renders knowledge which was known to no longer be:**

- a) **Accessible**
- b) **Findable** (whether one cannot find the knowledge or who has the knowledge)
- c) **Usable** (e.g., through missing context)

d) One simply does not know the knowledge exists

Like a hole in a bucket of water – what was once there and available is no longer able to be applied to the benefit of the product or process. And of note, it does not need to leak beyond a firm’s boundaries to cause a negative impact to a product or process, just out of control, memory or some other boundary. Perhaps this definition could be argued to be a subset of definition (i) above in that it represents a ‘knowledge and capability shortage’ at the point of need. Regardless, if knowledge is viewed as an asset, it should not be allowed to leak, just as one would not want money to unintentionally leak out of one’s bank account.

Challenge 4: Knowledge ‘leakage’ due to lack of structured and standardised knowledge management approaches. Knowledge was not findable or accessible when needed.

Challenge 5: Knowledge ‘leakage’ through loss of staff experience due to turnover. Knowledge dissipated and was not available when needed due to routine staff transitions, especially over the lengthy duration of the product lifecycle.

Challenge 6: The technology transfer itself caused obstructed knowledge flow (project context and/or process). This was due to certain knowledge transfer barriers between pharmaceutical development and commercial manufacture during technology transfer activities. Such barriers related to process complexity, low staff competency at the receiving site, differences in time zones, language issues, cultural differences, etc.

Furthermore, based on a review of the guidance documents, the researcher concluded that technology transfer is typically seen as a linear, once-through process. Given the absence of focus on KT to begin with, there is no evidence whatsoever to suggest a mechanism to reflect *if* and *how* knowledge transfer outcomes were achieved (or were not). Such a pause to reflect on progress to a plan would seem to be a valuable opportunity in pursuit of effective transfers, ongoing learning, and continual process improvement. A closed-loop **KT framework** – enabled by robust KM approaches – could address this gap and would in turn improve the corresponding technology transfer outcomes. This is supported by the literature (Malik, 2002; Kremic, 2003) suggesting

that knowledge transfer during technology transfer should include a feedback loop to ensure the effectiveness of KT and a learning opportunity for the sending site.

6.2.2 Defining requirements for a technology transfer knowledge transfer framework

Having identified the key challenges believed to cause ineffective KT during technology transfer, the research focus turned toward exploring the requirements for a KT framework to proactively prevent this loss of critical knowledge. First, returning to the six challenges to KT identified previously and employing a CTQ tree²⁸, five high-level requirements of a **KT framework** were identified and listed below (I-V):

- I. Knowledge transfer is guided by an intentional and robust plan
- II. Knowledge transfer is best enabled by a culture that values knowledge as an asset
- III. Standardised approaches for KM are established both for explicit and for tacit knowledge
- IV. Tacit knowledge is uncovered and transferred during technology transfer
- V. Knowledge transfer effectiveness is measured and an action plan to address any gaps and opportunities is prepared

From the five high-level requirements, 16 detailed requirements were identified to provide further granularity of solution requirements. While the five high-level requirements essentially act as principles, these next level requirements were identified to be more specific and actionable. These were grouped as follows:

- Knowledge to be transferred
- Knowledge transfer process
- Knowledge flow enablers and detractors
- Degree of change from sending unit to receiving unit

Further details on the requirements and processes used to define them can be found in the referenced peer-reviewed paper (Lipa, Greene and Calnan, 2021). A summary

²⁸ A **CTQ tree** or, Critical to Quality tree, is a technique used to identify the needs of the customer (i.e., the outputs from a process) and translate the needs into measurable product and process requirements (Six Sigma Daily, no date)

diagram linking the problem statement to the detailed requirements is provided in Figure 6-3.

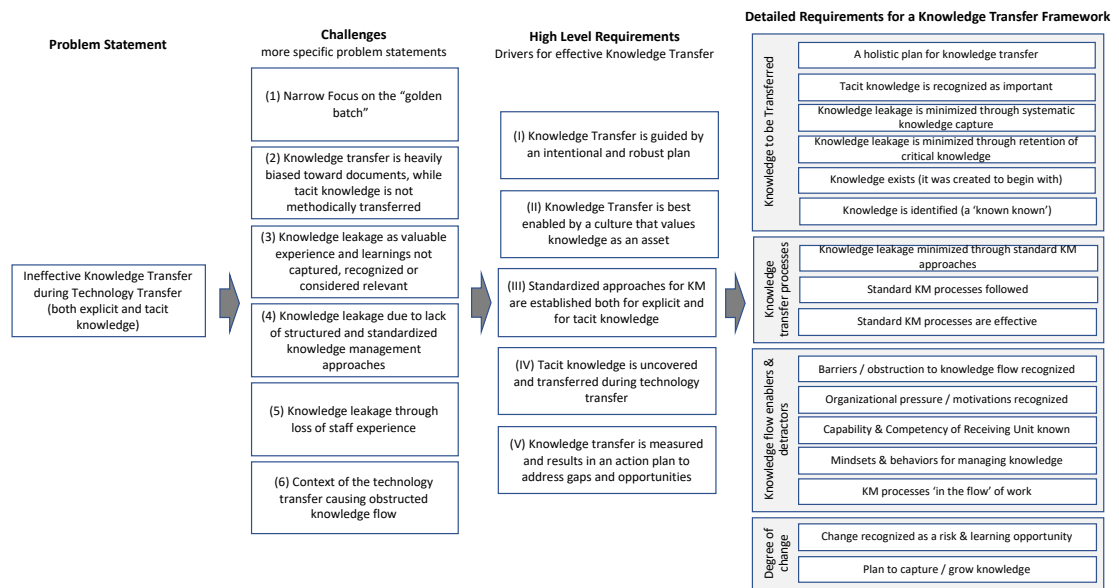


Figure 6-3 – Mapping problem statement to requirements for a technology transfer knowledge transfer framework

6.3 Evaluation of knowledge transfer framework requirements

With the KT problem better defined and the solution requirements preliminarily identified, it was a good opportunity to pause and benchmark against the findings from the literature review. In the absence of a definitive framework, recall Ward et al. (Ward, House and Hamer, 2009) conducted a study of existing frameworks for knowledge transfer and inventoried 28 generalised frameworks in the literature and identified five common components. They then proposed a conceptual framework embodying those five common components including:

- the problem
- the knowledge
- the context barriers or supports
- the interventions
- the utilisation

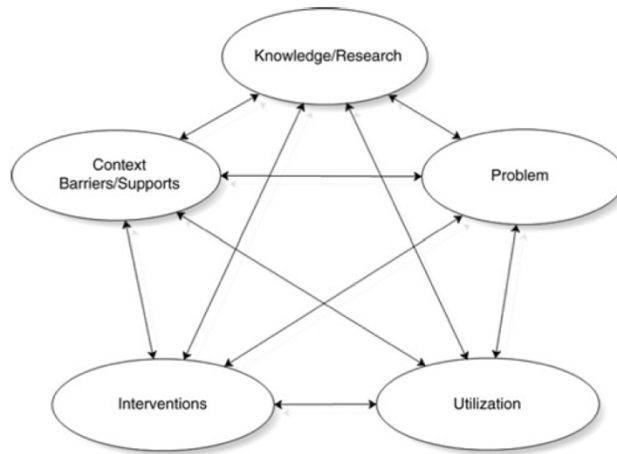


Figure 6-4 – Conceptual framework of the knowledge transfer process (Ward, House and Hamer, 2009)

A gap assessment of the KT framework *requirements* proposed by the researcher (depicted in Figure 6-3) was conducted against the proposal by Ward et al. The assessment result is shown in Table 6-1, as a means to evaluate whether the requirements are complete in addressing all components identified by Ward et al. (Ward, House and Hamer, 2009).

Table 6-1 – Proposed requirements by researcher vs. conceptual knowledge transfer framework by Ward et al. (Ward, House and Hamer, 2009)

Component from conceptual framework	How researcher’s technology transfer knowledge transfer framework addresses this component	Addressed in Researcher Framework Requirements?
Problem	The subject technology transfer with associated context, assessed by the holistic plan for knowledge transfer	Yes
Knowledge	Knowledge to be transferred (requirements grouping)	Yes
Context barriers or supports	Knowledge flow enablers & detractors (requirements grouping), degree of change (requirements grouping)	Yes
Interventions	Knowledge transfer processes (requirements grouping)	Yes
Utilisation	The subject technology transfer with associated progress versus technology transfer plan, including assessment by the holistic plan for knowledge transfer outcomes of the technology transfer and sustained performance,	Yes

While highly qualitative, the detailed KT framework requirements derived independently within this thesis are verified to address all five common components of KT frameworks found in the literature, suggesting this set of requirements addresses all key components commonly found in KT frameworks.

Armed with this basic understanding of the needs of a solution, the researcher proceeded to develop a framework to enhance KT during technology transfer, the details of which are discussed in Chapter 7.

Chapter 7: A Proposed Framework and Toolkit to Enhance Knowledge Transfer during Technology Transfer

The purpose of this chapter is to present a framework to enhance the effectiveness of KT during technology transfer, the *Knowledge Transfer Enhancement Framework*, or *KT^E Framework*. The framework is further supported by a corresponding toolkit, the *KT^E Toolkit* which is also presented. This section is presented as a summary of a peer-reviewed paper published in the *PDA Journal of Pharmaceutical Science and Technology* (Lipa, Greene and Calnan, 2021).

In addition to the framework and toolkit, this chapter also provides supporting materials for implementation of the framework, including a mapping of the framework to the technology transfer process and a high-level metrics plan.

7.1 A knowledge transfer framework for pharmaceutical technology transfer

Having identified the detailed requirements in Chapter 6 (section 6.2) and given the desire to have a simple, closed-loop process that was both widely known and pragmatic in nature, the researcher selected the PDCA, or *Plan-Do-Check-Act* model, as a starting basis to build upon. This model made popular by Deming (ASQ, 2019) is an iterative and cyclical means to improve a given process.

To leverage the cyclical nature of the PDCA and make the framework more relevant to KT during technology transfer, the intent and description of each stage was adapted as follows and depicted in Figure 7-1 which is presented as the *Framework for Knowledge Transfer Enhancement*, or *KT^E Framework*:

1. **Knowledge Transfer (KT) Readiness Planning** (Plan)
2. **KT Execution** (Do)
3. **KT Effectiveness Assessment** (Check)
4. **KT Action Plan** (Act)

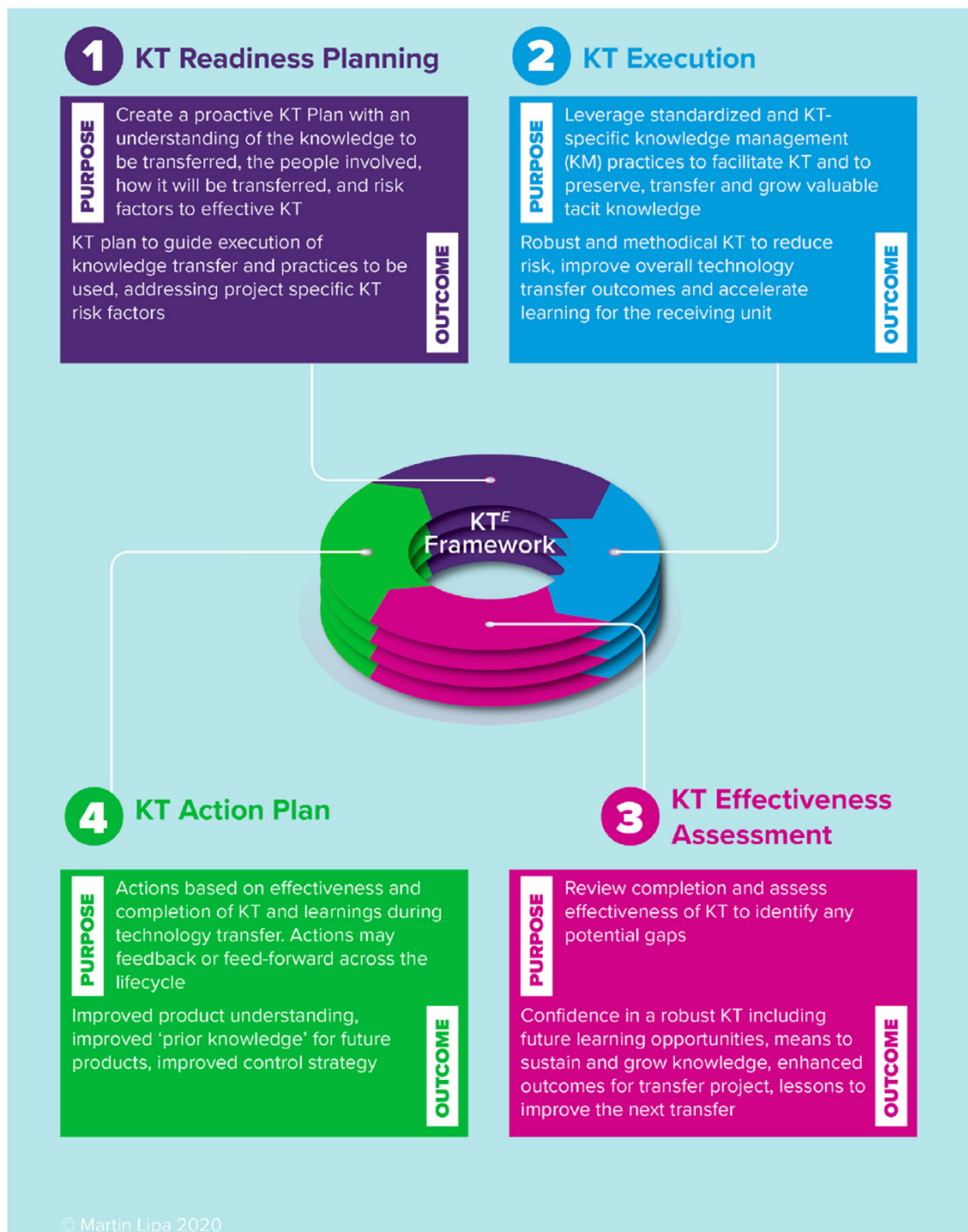


Figure 7-1 – The KT^E Framework on a page

The referenced paper (Lipa, Greene and Calnan, 2021) by the researcher includes further details on each stage of the KT^E Framework.

7.2 A knowledge transfer toolkit for pharmaceutical technology transfer

Supporting the *KT^E Framework* is a *KT^E Toolkit*, consisting of a series of practices to support the ‘how’ behind knowledge transfer. These KM practices are introduced in the referenced peer-reviewed paper (Lipa, Greene and Calnan, 2021). Table 7-1, *KT^E Toolkit on a Page*, provides a listing of the tools and practices, a brief intent statement for each (“Use it to...”), and next steps to implement each tool or practice, which in some cases may involve future research study. While further development of this toolkit will certainly be of value through thoughtful definition and identification of proven practices, in the opinion of the researcher with the intent of each framework stage and tool defined, organisations should feel empowered to start to address these gaps on their own.

Table 7-1 – KTE Toolkit on a Page

KTE Stage KTE Tool	Use it to...	Next steps to implement tool / practice
KT Readiness Planning		
1.1 – KT Risk Factor Assessment	Reduce risk to technology transfer	Define through future study; Based on socialisation of these concepts of knowledge transfer challenges, organisations can immediately incorporate into technology transfer risk assessments
1.2 – KT Plan	Build knowledge transfer into technology transfer	Basic outline to define knowledge to be transferred (e.g., from knowledge map) and how (KM/KT practices to be utilised and built into project) can be immediately built into technology transfer plans or supporting knowledge transfer plans. This should include a plan for appropriate training. Future study to define a template would likely be of benefit.
1.3 – KT Mindsets & Behaviours	Create shared team understanding of the need to manage knowledge as an asset	These concepts are preliminary explored in Chapter 9 and warrant future study
KT Execution		
2.1 – KT Community of Practice (CoP)	KM best practice to standardise knowledge flow	Best practices for CoPs exist (Kane and Lipa, 2018); Define tech transfer-specific CoP through future study
2.2 – Standard KM Practices	KM best practice(s) to standardise knowledge flow	Many common practices exist and can be applied (Kane and Lipa, 2018; ISPE, 2021b)
2.3 – KT Knowledge Map	Identify knowledge to be transferred	Define through future study; basic expectations exist via BPOG Knowledge Map (BioPhorum Operations Group, 2020) and explicit document lists found in ISPE (ISPE, 2018), PDA (PDA, 2014b) and other technology transfer guidance documents
2.4 – KT ‘What if’ Assessment	KM practice to surface and transfer tacit knowledge	Refer to <i>Simple Practices</i> paper (Lipa, Kane and Greene, 2020)
2.5 – Tech Transfer Knowledge Sharing	KM practice to surface and transfer tacit knowledge, enable rapid continual improvement	Refer to <i>Simple Practices</i> paper (Lipa, Kane and Greene, 2020)
KT Effectiveness Assessment		
3.1 – Explicit KT Checklist	KM best practice to standardise knowledge flow	Audit against KT Plan and knowledge map
3.2 – Tacit Knowledge Turnover	KM practice to surface and transfer tacit knowledge	Refer to <i>Simple Practices</i> paper (Lipa, Kane and Greene, 2020)
3.3 – Lessons Learned	KM best practice – use to surface and transfer tacit knowledge & foster continual improvement	Leverage existing proven practices for Lessons Learned / After Action Review (ISPE, 2018; Kane and Lipa, 2018)
3.4 – KT Summary Report	Assess completion of KT	Audit against goals in KT Plan and completion of items 3.1 through 3.3
KT Action Plan		
4.1 – KT Action Plan	Act on learnings, including process improvement, knowledge capture and informing control strategy	Basic action plan resulting from above actions, including open items from knowledge transfer summary report, actions identified during tacit knowledge transfer and lessons learned
4.2 – Receiving Unit KM Plan	KM best practices to maintain and grow transferred knowledge at RU	KM plan for the receiving unit to sustain and grow product knowledge; Potential to define through future study

One area in particular the researcher explored was that of tacit knowledge transfer. Given the general neglect of tacit knowledge (as characterised multiple times in previous chapters), the researcher had an interest in advancing the dialogue on meaningful tacit knowledge transfer techniques, while also creating a model for several of the tools proposed in the *KT^F Toolkit*. The results are captured via a case study in a paper by the author, *Simple Practices to Facilitate the Flow of Valuable Tacit Knowledge during Biopharmaceutical Technology Transfer: A Case Study* (Lipa, Kane and Greene, 2020). This case study was also presented as part of a presentation at the 2021 PDA Annual Meeting (Lipa, 2021a) and is featured in the *ISPE Good Practice Guide on Knowledge Management* (ISPE, 2021b).

In summary, the researcher, while involved with a complex technology transfer for a multi-valent vaccine, led the design of two tacit knowledge transfer practices (*Technology Transfer Batch Execution Review* and *Tacit Knowledge Turnover Assessment*) and consulted on a third (*What if...?*). Drawing on best practices in KM, each of the tacit knowledge transfer practices share common elements, including:

- Standardised business processes for knowledge capture and transfer (and codification to explicit knowledge, where appropriate)
- Basic governance to ensure prioritisation and follow through on important actions
- Enabling mindsets for sending and receiving site personnel, including ‘safe to share’ and a sense of inquisitiveness, including active engagement and participation from people, such as experts from the sending site and members from the receiving site

The general process for *Technology Transfer Batch Execution Review* is illustrated in Figure 7-2, highlighting a relatively simple set of questions that can be pursued before and after batch execution to create meaningful dialogue, ideas, questions, and exchange of information. Coupled with the common elements (e.g., governance), these processes were highly effective in generating valuable insights.

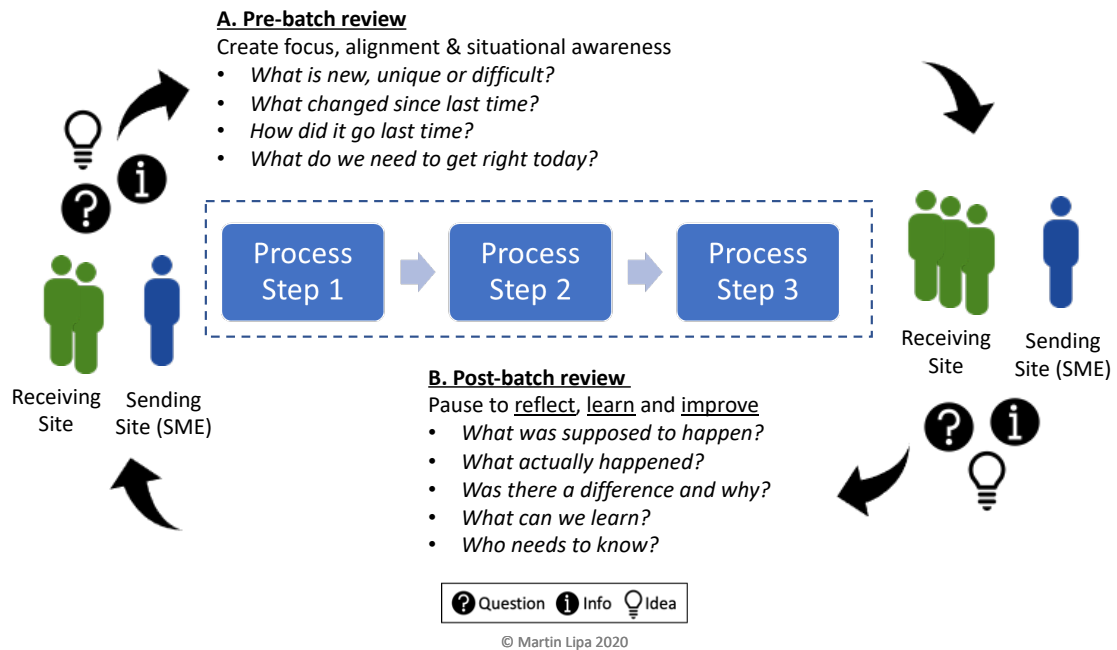


Figure 7-2 – Technology Transfer Batch Execution Review

These three tacit knowledge transfer processes delivered significant positive impact to the success of the technology transfer in reducing cost and risk through proactive learning and improved right-first-time execution. *Technology Transfer Batch Execution Review*, for example, resulted in 52 proactive actions which in turn prevented 43 potential deviations in the quality system. Furthermore, there was overwhelmingly positive stakeholder feedback on the contribution of this process to continual improvement ‘on a near real-time basis.’ This practice and the other two tacit knowledge transfer processes are presented in further detail in the referenced paper (Lipa, Kane and Greene, 2020).

7.3 Feedback on the KT^E Framework

Importantly, the KT^E Framework was not developed in a vacuum. In addition to the experiences of the researcher, the framework was informed by the literature, the current state assessment and resulting derived requirements, and by feedback via interviews. Interviews to solicit feedback on a preliminary iteration of the KT^E Framework were conducted between December 2019 and February 2020 to solicit feedback from industry SMEs on technology transfer, senior leaders, and a regulatory authority. The intent was to gain insights on potential benefits from the framework,

whether the framework was logical, and whether it was workable (i.e., practical to implement).

7.4 Practical application of the KT^E Framework to technology transfer

To demonstrate the application of the KT^E Framework and associated KT^E Toolkit to a technology transfer project, the researcher leveraged a five-step overview of the technology transfer process described by Abraham et al. (Abraham *et al.*, 2015) to create the following process flow.

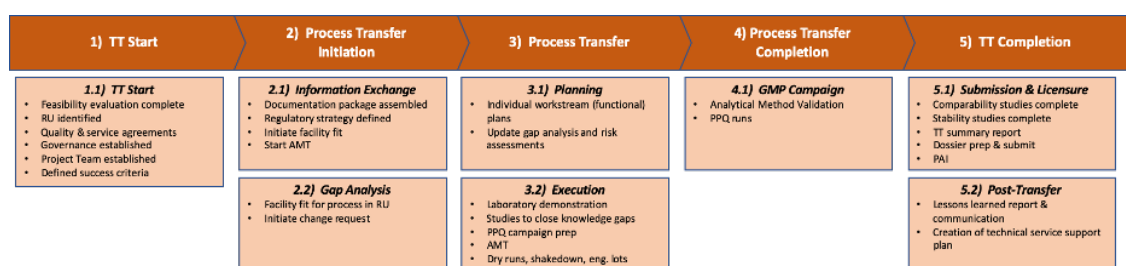
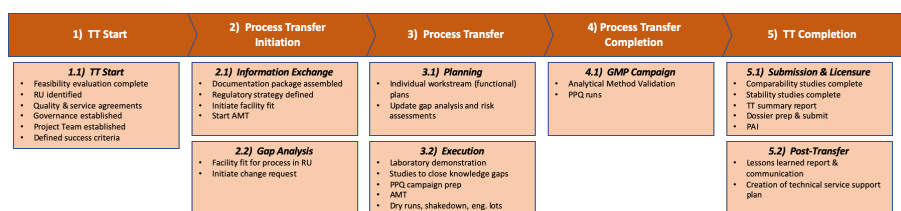


Figure 7-3 – Key activities and milestones in biopharmaceutical technology transfer

Using the technology transfer flow steps as headings, a matrix was developed by the researcher and is shown in Figure 7-4. Beneath each of the five steps of the technology transfer process, a mapping of the respective KT^E stages and KM practices are presented.



STAGE 1: KT PLANNING	RISK FACTOR ASSESSMENT	●				
	KT PLAN	●				
STAGE 2: KT EXECUTION	MINDSETS & BEHAVIORS	●	●	●	●	●
	TECH TRANSFER COP	●	●	●	●	●
	STANDARD KM	●	●	●	●	●
	KNOWLEDGE MAP		●			
	"WHAT IF...?"			●	●	
STAGE 3: KT EFFECTIVENESS ASSESSMENT	TT KNOWLEDGE SHARING			●	●	
	EXPLICIT K CHECKLIST					●
	TACIT KNOWLEDGE TURNOVER					●
	LESSONS LEARNED					●
STAGE 4: KT ACTION PLANNING	KT SUMMARY REPORT					●
	KT ACTION PLAN					●
	RECEIVING UNIT KNOWLEDGE MANAGEMENT PLAN	●				●

Figure 7-4 – A matrix indicating where the KT^E Framework and KT^E Toolkit can be applied to the technology transfer process

7.5 Metrics for the KT^E Framework

A measurement system is critical to ensure an objective is achieved and to provide a tangible means to assess progress. The ultimate outcome of an effective KT is in support of the goals of ICH Q10 (ICH, 2008) and informing QRM to, in turn, reduce risk to patients (Chapter 5). However, in practice, measurement of these outcomes is difficult since they come along after the technology transfer is complete, and they are often confounded with other improvement initiatives (i.e., improvements often cannot be attributed *specifically* to KT effectiveness). Also, in the experience of the researcher, success in KM is often about what *didn't happen* rather than what *did happen* in the future (said differently, with effective KM, issues can be averted or solved quickly and risks can be managed before major issues occur, therefore attribution to the success of KM can be difficult to establish).

It is envisaged that the KT^E Framework will be primarily measured by a set of *leading* metrics proposed by the researcher, intended to assess progress and activity in applying the framework. These metrics are typically considered *leading* indicators as they are *predictive* in nature of an outcome. In the case of the KT^E Framework, the research activities to determine the current state and challenges with technology transfer KT (Chapter 6) have already established the impact of *not* having structured KT approaches

in place. Therefore, metrics tied to the *KT^E Framework* deployment can establish an initial baseline to demonstrate structured KT approaches. When used, they can provide a degree of confidence in improving both KT and technology transfer outcomes. It is fully anticipated these metrics will evolve and be refined over time based on feedback. A preliminary metrics plan for the *KT^E Framework* is listed in Table 7-2.

Table 7-2 – *KT^E Framework metrics plan*

Leading Indicator	Target Value
Knowledge transfer Plan: plan in place and approved, including KT Risk Factor Assessment and KT Readiness Assessment	Yes
Knowledge transfer plan: progress to plan	Execution is on plan (scope and schedule)
Team enrolled in knowledge transfer mindsets and behaviours, through onboarding, team chartering or other appropriate means	>95% enrolled
Knowledge management maturity at sending site	At least standardised (mid-level maturity)
Knowledge management maturity at receiving site	At least standardised (mid-level maturity)
Closure of knowledge-related actions identified during technology transfer (e.g., those identified during risk assessments and tacit knowledge transfer exercises such as <i>What If?</i> and <i>Tacit Knowledge Turnover</i>)	>90% of high priority items closed within 3 months
Closure of actions from lessons learned / after action reviews conducted in-process during technology transfer and at the conclusion of technology transfer	>90% of high priority items closed within 3 months
Closure of actions identified in Knowledge Action Plan , including feedback and feed forward actions on the transferred product and process, as well as on the business processes of technology and knowledge transfer	>90% of high priority items closed within 3 months
Knowledge transfer completion is measured as part of overall technology transfer metrics	Yes
<i>KM-practice specific measures, as appropriate based on KM practices selected</i>	<i>Varies, based on knowledge management practices applied.</i>

Lagging indicators, which indicate past performance, can also be used for technology transfer outcomes, are listed in Table 7-3. Due to the latency to measure such outcomes, a mix of leading and lagging measures is recommended.

Table 7-3 – Lagging measures for technology transfer using the KT^E Framework

Lagging Indicator	Target <i>directional and qualitative, relative to company's baseline performance</i>
Deviations during PPQ	Fewer deviations
Process reproducibility	Increased reproducibility
Process robustness / performance	Increased robustness performance
Measures of risk reduction for successful technology transfer	Lower residual risk
Technology transfer completed on schedule	Tighter schedule adherence
Technology transfer completed on budget	Tighter budget adherence

7.6 Summary – KT^E Framework

In summary, the KT^E Framework presented in this chapter is positioned as one potential solution to improve KT during technology transfer. This framework has been based on learnings from the literature, other KT models, a well-informed set of requirements, feedback from industry experts, leaders and regulatory authorities, peer reviewers of the related paper, and the experience of the researcher. Further information on how the KT^E Framework provides a means for feedback (e.g., to inform future transfers) and feed-forward (e.g., to inform the control strategy) is explored in the referenced paper (Lipa, Greene and Calnan, 2021).

Part three which follows, including Chapters 8 and 9, which explored how the RKI Cycle could be applied across the product lifecycle to extend its reach and impact.

Part Three: The *RKI Cycle* across the Product Lifecycle and Knowledge Culture as a Catalyst

Part Three demonstrates how the *RKI Cycle* can be applied across the product lifecycle, including:

- Three examples with a focus on each KM across the product lifecycle, change management during commercial manufacturing, and the link between QRM, KM and data analytics (Chapter 8).
- This part also explores the concept of *knowledge culture*, including a review of current cultural issues which are barriers to knowledge management in the pharmaceutical industry, existing definitions of knowledge culture outside of the pharmaceutical industry, and benchmarking the corollary of *quality culture*. This section concludes with proposing a preliminary 'ideal knowledge culture' (Chapter 9).

Chapter 8: Demonstrating How the *RKI Cycle* Can be Applied Across the Product Lifecycle

Given the findings of this research on the importance of connecting QRM and KM and ensuring the effective management of knowledge – coupled with the evidence that this is not done well in practice today – an important opportunity to maximise the impact of these findings is presented. The purpose of this chapter is to demonstrate examples of how the *RKI Cycle* can be applied across the product lifecycle as depicted in ICH Q10 (ICH, 2008) (Figure 8-1).



Figure 8-1 – The product lifecycle as depicted by ICH Q10 (ICH, 2008)

The first of three examples focuses on managing knowledge across the product lifecycle to ensure knowledge availability for managing risk (in addition to operational benefits). This first example takes a broad view across all four stages of the end-to-end product lifecycle and is centred primarily on node 5 of the *RKI Cycle* (Figure 8-2, as presented in Chapter 5 and the related peer-reviewed paper (Lipa, O'Donnell and Greene, 2020a).

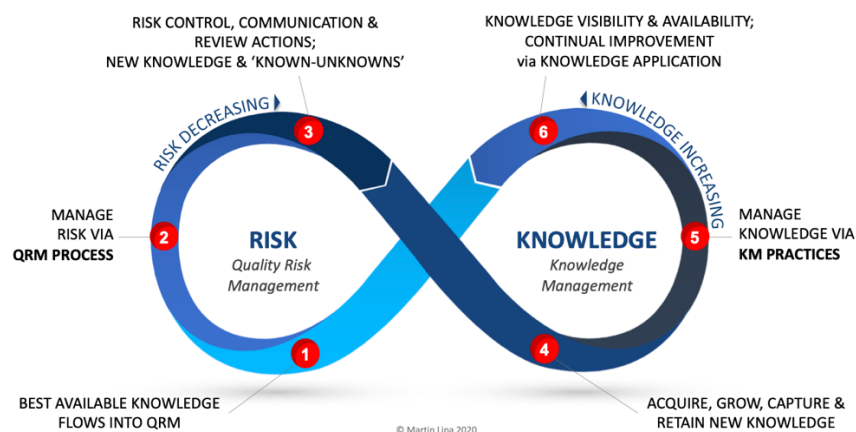


Figure 8-2 – The Risk-Knowledge Infinity Cycle as applied to ICH Q10

The second example features an application of the *RKI Cycle* within a single lifecycle stage, the commercial manufacturing stage of the product lifecycle. Specifically, this

example highlights the PQS element of *change management* and illustrates how the *RKI Cycle* is ‘continuous and perpetual’ (Chapter 5, section 5.2). This example presents four common change triggers flowing through the *RKI Cycle*, each starting at a different node, either 1, 3, 4, or 6 (Figure 8-2).

The third example demonstrates how the *RKI Cycle* can provide a tangible mechanism for data analytics to *generate knowledge* and *enable risk reduction*, by injecting new knowledge derived from data analytics into node 4 (Figure 8-2).

These first two examples have been published in two separate papers and are summarised in the following sections of this chapter. The first paper which maps stage-appropriate KM methods and tools across the lifecycle was published in *Level3* (Lipa and Kane, 2021) and subsequently used in Chapter 5 of the *ISPE Good Practice Guide on Knowledge Management* (ISPE, 2021b). At the time of this thesis submission, the second paper featuring the *RKI Cycle* for change management during commercial manufacturing has been accepted by ISPE and is planned to be released in May 2021 as the subject of a global webcast (Lipa and Mulholland, 2021). The third example was the subject of a presentation given by the researcher at the launch of the *Guide to Data Analytics for Pharmaceutical Manufacturing* (PMTTC, 2020) by the Pharmaceutical Manufacturing Technology Centre²⁹.

8.1 Managing knowledge across the product lifecycle (Example 1)

A key concept inherent in the product lifecycle is that knowledge will grow over time through planned (e.g., development studies, prospective process changes) and unplanned (e.g., investigations, risk control failures) activities. A key tenant of the *RKI Cycle* is that knowledge should be effectively managed (at node 5) to ensure it is available and can be applied to reduce risk and support continual improvement (as illustrated by Figure 5-5).

²⁹ The Pharmaceutical Manufacturing Technology Centre (PMTTC), <http://www.pmtc.ie>

To date, this thesis has focused on the technology transfer stage of the product lifecycle. Stepping back to take the entire product lifecycle into account, one can envision that knowledge is increasing at every stage as depicted in Figure 8-3. This depiction by no means suggests there are a finite number of RKI cycles for the four lifecycle stages; rather, this RKI cycle is always repeating ('continuous and perpetual') across the product lifecycle.

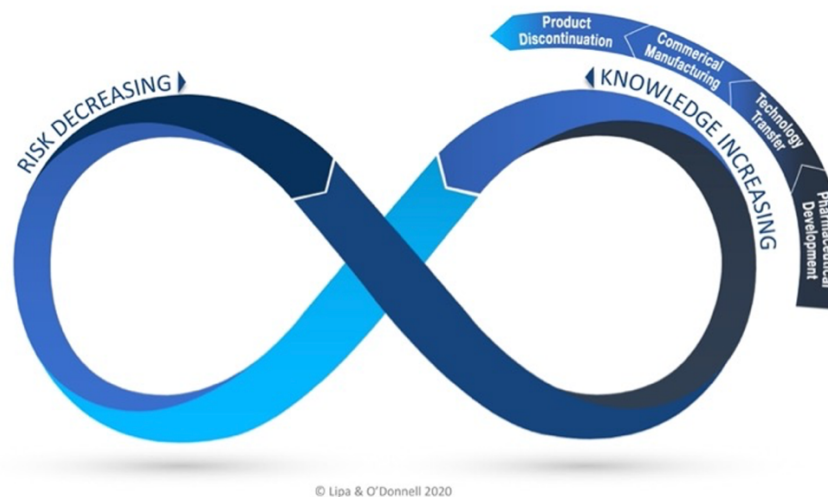


Figure 8-3 – The RKI Cycle as knowledge increases across the product lifecycle

One might expect the emphasis of KM plans and practices to vary slightly from stage to stage based on the applicable knowledge-intensive activities in each stage. The following sections consider each of the lifecycle stages separately, including considerations of each phase introduced by Kane's PPKL model (Kane, 2018) as introduced in Chapter 2 (section 2.1.3.1).

8.1.1 Pharmaceutical Development

Considering *Pharmaceutical Development*, labelled as *Product Development* in the PPKL model (Kane, 2018), examples of knowledge-related activities include (ISPE, 2011):

- Application of prior knowledge for risk assessments to determine areas of study
- Development work to capture new knowledge
- Ongoing risk assessment and risk control

Knowledge management should be a key enabler to *Product Development* through standardised methods and tools delivering on the following capabilities:

- Access to prior knowledge (platform technologies, other products, expertise in the company (individuals & CoEs), external scientific literature, prior learnings & lessons, etc.)
- Capture of new knowledge during early development work (both what worked and what did not), including both explicit and tacit knowledge
- The record of product development, including scientific knowledge, supporting design choices, and other decision rationale

8.1.2 Technology Transfer

Considering *Technology Transfer* (*new product introduction* and *In-line transfers*), examples of knowledge-related activities (WHO, 2011; PDA, 2014b; ISPE, 2018), as explored in detail in Chapter 6, include:

- Application of knowledge for risk assessments
- Comprehensive knowledge transfer, including tacit knowledge
- Opportunity to learn more about the product and process
- Supporting the goal to ensure a right-first time transfer, robust process and a fully capable receiving site

Knowledge management should be a key enabler to *Technology Transfer* through standardised methods and tools delivering the following capabilities, as explored in detail in Chapter 7:

- Access to comprehensive product and process knowledge, including development and manufacturing history (e.g., key decisions, learnings from failures, changes, etc.)
- Access to subject matter experts / personnel with process experience
- Capture of new learnings including increased knowledge and understanding of product/process, lessons learned, etc.

8.1.3 Commercial Manufacturing

Considering *Commercial Manufacturing* (inclusive of *Continual Improvement*) examples of knowledge-related activities include (ICH, 2008):

- Ongoing knowledge build through accumulated manufacturing experience
- Lifecycle management, including planned and unplanned changes
- Seeking to minimise disruptions to product availability by rapid problem solving and solving problems at root cause

Knowledge management should be a key enabler to *Commercial Manufacturing* through standardised methods and tools delivering the following capabilities:

- **Capture of new learnings**, including increased knowledge and understanding of product/process, lessons learned, etc.
- **Knowledge visibility and availability** across the full product lifecycle (including development) to ensure broad access to knowledge to support process monitoring, continual improvement, change management, investigations, etc.
- **Support for problem solving and sharing of best practices and improvements** across the supply chain and back to development organisation

8.1.4 Product Discontinuation

Considering *Product Discontinuation*, examples of knowledge-related activities include (ICH, 2008):

- Knowledge transfer for archival and future access on demand
- Harvesting learnings to inform 'prior knowledge'

Knowledge management should be a key enabler to *Product Discontinuation* through standardised methods and tools delivering the following capabilities:

- **Capture of knowledge in a complete and structured manner** to allow for future access (e.g., stability, complaints, etc.)
- **Capture of learnings** including insights for platform knowledge and other potential 'prior knowledge'

Given these high-level understandings of the necessary knowledge capabilities for each stage of the product lifecycle, the researcher suggested suitable KM methods and tools can be applied to each stage, which are presented in the next section.

8.1.5 Product lifecycle stage-appropriate KM methods and tools to ensure knowledge availability

The researcher suggested that current established KM methods and tools can be employed to provide the necessary means to effectively manage knowledge in a standardised and consistent manner, ensuring the best possible knowledge is available to maximise the reduction of risk via the *RKI Cycle*.

To illustrate this, Table 8-1³⁰, created by the researcher, provides a preliminary mapping of KM methods and tools required to satisfy the conceptual needs of each product lifecycle stage. This table has been accepted by the *ISPE Good Practice Guide on Knowledge Management* SME author team and is featured in Chapter 5 of the ISPE Guide. Following Table 8-1, a description for each KM method or tool is provided in Table 8-2.

³⁰ Note – column heading labels have been adjusted post-publication in *Level3* to improve clarity of the text as it relates to this thesis

Table 8-1 – Stage-appropriate KM methods & tools across the product lifecycle

Lifecycle Stage	Knowledge-related activities (activities where knowledge is required)	Knowledge Capabilities Required (How Knowledge Management can provide benefit)	KM Methods & Tools																		
			Planning & Requirements Definition					Mostly Explicit-based				Mostly Tacit-based				Enabling elements					
			KM Maturity Assessment	Knowledge Mapping	Product KM Plan	Knowledge Transfer Plan	Site / Functional Area KM Plan	Content Management	Taxonomy & Search	Platform Knowledge Base	Product Knowledge Base	Communities of Practice	After Action Review / Lessons Learned	Expertise Location	Decision Rationale Capture	Tacit Knowledge Retention & Transfer Practices	KM Roles	KM Training	Knowledge-valuing culture	Sponsorship, Governance, Metrics & Other enablers	
		<p>Note 1: Illustrative concepts, not an exhaustive listing</p> <p>Note 2: References below to knowledge refer to both explicit and tacit knowledge</p> <p>Note 3: Additional concepts or complexity may be introduced when multiple entities are involved</p>																			
Product Development	<ul style="list-style-type: none"> - Application of prior knowledge for risk assessments to determine areas of study - Development work to capture new knowledge - Ongoing risk assessment and risk control 	Common KM elements for <i>Product Development</i> phase	X	X													X	X	X	X	
		Access to prior knowledge (platform technologies, other products, expertise in the company (individuals & CoEs), external scientific literature, prior learnings & lessons, et al)						X	X	X	X	X	X								
		Capture of new knowledge during early development work (both what worked and what didn't)			X	X		X	X	X	X		X		X						
		The record of product development, including scientific knowledge and supporting design choices and other decision rationale			X	X		X	X	X	X		X		X	X					
New Product Introduction / Technology Transfer	<ul style="list-style-type: none"> - 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 	Common KM elements for <i>Technology Transfer</i> phase		X													X	X	X	X	
		Access to comprehensive product and process knowledge, including development and manufacturing history, including key decisions, learnings from failures, changes, etc.			X	X	X	X	X	X	X	X	X	X	X	X					
		Access to subject matter experts / personnel with process experience				X			X			X		X		X					
		Capture of new learnings including increased knowledge and understanding of product/process, lessons learned, etc.			X	X	X	X		X	X	X	X		X	X					
Commercial Manufacturing / Continuous Improvement	<ul style="list-style-type: none"> - 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 	Common KM elements for <i>Commercial Manufacturing</i> phase	X	X													X	X	X	X	
		Capture of new learnings including increased knowledge and understanding of product/process, lessons learned, etc.			X	X	X	X	X	X	X	X	X		X	X					
		Knowledge visibility and availability across the full product lifecycle (including development) to ensure broad access to knowledge to support process monitoring, continual improvement, change management, investigations, et al			X	X	X	X	X	X	X	X	X	X	X	X					
		Support for problem solving and sharing of best practices and improvements across the supply chain and back to development organization			X	X	X	X	X	X	X	X	X	X							
Product Discontinuation	<ul style="list-style-type: none"> - Knowledge transfer for archival and future access on demand - Harvesting learnings to inform 'prior knowledge' 	Common KM elements for <i>Product Discontinuation</i> phase		X													X		X	X	
		Capture of knowledge in a complete and structured manner to allow for future access (e.g. stability, complaints, etc.)			X			X	X		X		X	X	X	X					
		Capture of learnings including insights for platform knowledge and other potential 'prior knowledge'				X				X		X	X	X	X						

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Table 8-2 – Description of KM methods & tools

KM Method or Tool	Description
Planning & Requirements Definition	
KM Maturity Assessment	A means to objectively measure maturity of KM effectiveness based on various attributes such as process, culture, technology, etc.
Knowledge Mapping	A structured means to document the knowledge needed for a business process, a functional group, a role, etc. Used to understand knowledge requirements and identify gaps.
Product KM Plan	A strategy document to define the plan for how the knowledge associated with a product will be managed across the lifecycle of the product.
Knowledge Transfer Plan	A strategy document to define the plan for how the knowledge transfer will be managed.
Site / Functional Area KM Plan	A strategy document to define the plan for how the knowledge associated with a site or functional group will be managed.
Mostly Explicit-based	
Content Management	A structured ³¹ means to manage documents and other explicit knowledge (e.g., videos, pictures, etc.). Typically includes the end-to-end lifecycle of content (e.g., creation, tagging, storage, delivery). Applies to both GMP and non-GMP content which may be managed in separate systems.
Taxonomy & Search	Taxonomy is a structured means to describe and tag content (and potentially other features such as synonyms, semantics, etc.), and a means to deliver results through a robust, integrated search enabled by such a taxonomy.
Platform Knowledge Base	A structured means to define the scope of platform knowledge (explicit and tacit) and corresponding approaches to manage this in a consistent way to ensure knowledge visibility and availability across the product lifecycle.
Product Knowledge Base	A structured means to define the scope of product knowledge (explicit and tacit) and corresponding approaches to manage this in a consistent way to ensure knowledge visibility and availability across the product lifecycle.
Mostly Tacit-based	
Communities of Practice	A structured means to connect groups of people with a shared need or interest
After Action Review / Lessons Learned	A structured means to surface learnings from the experiences of people, often associated with a project or other business process, and subsequently capture and implement these learnings to support continual improvement.
Expertise Location	A structured means to identify important expertise and/or experience in the organisation and connect to it on demand.
Decision Rationale Capture	A structured means to capture decision rationale and ensure it is available in the future when needed.
Tacit Knowledge Retention & Transfer Practices	A variety of structured means to identify, prioritise, transfer and retain tacit knowledge (i.e., 'know-how' and other knowledge 'in people's heads')
Enabling Elements	
KM Roles	Standardised roles for managing knowledge consistently, such as community stewards, KM leads, and others.
KM Training	Training on appropriate KM topics to build awareness and competency of individuals in the organisation.
Knowledge-valuing culture	Mindsets and behaviours which value the knowledge of the organisation as an asset (e.g., capturing and sharing lessons, seeking to leverage prior knowledge)
Sponsorship, Governance, Metrics & Other enablers	Best practices to enable effective and sustainable KM.

³¹ Structured = Standardised and inclusive of people, process, technology, and governance

The capabilities and corresponding mapping of KM methods and tools presented in Table 8-1 and Table 8-2 above is preliminary in nature and based on the experiences of the researcher. While an in-depth study was conducted for technology transfer (Chapter 6 and Chapter 7), resulting in the *KT^E Framework* and *KT^E Toolkit*, defining additional requirements for the other three lifecycle stages (i.e., product development, commercial manufacturing, and product discontinuation) would further expand this research and suitable frameworks for the other three stages could be developed.

8.2 *RKI Cycle* application to change management during commercial manufacturing stage (Example 2)

While the previous section on managing knowledge across the product lifecycle illustrated an end-to-end application of the *RKI Cycle*, this second example focuses more in depth on change management during commercial manufacturing.

Commercial manufacturing is typically the longest stage of the product lifecycle and as such provides an abundance of opportunities for knowledge capture, flow, and application across numerous activities. ICH Q10 lists four PQS elements (ICH, 2008) that are substantially dependent on the application of QRM and KM, as *Process Performance and Product Quality Monitoring*, *Corrective Action / Preventative Action (CAPA)*, *Change Management* and *Management Review of Process Performance and Product Quality*. Effective change management is central to the achievement of one of the objectives of ICH Q10, being the objective of continual improvement. Thus, change management 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.

The triggers for change management may vary as described in a recent PIC/S recommendation paper (PIC/S, 2019), which lists examples of potential change triggers (or reasons to raise a change proposal), as follows:

- 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 initiatives

The list above gives a diverse range of reasons for triggering a change. Some changes are 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 (Mulholland and Greene, 2020). At a practical level, these differences mean that the change proposals can commence at different nodes on the *RKI Cycle*.

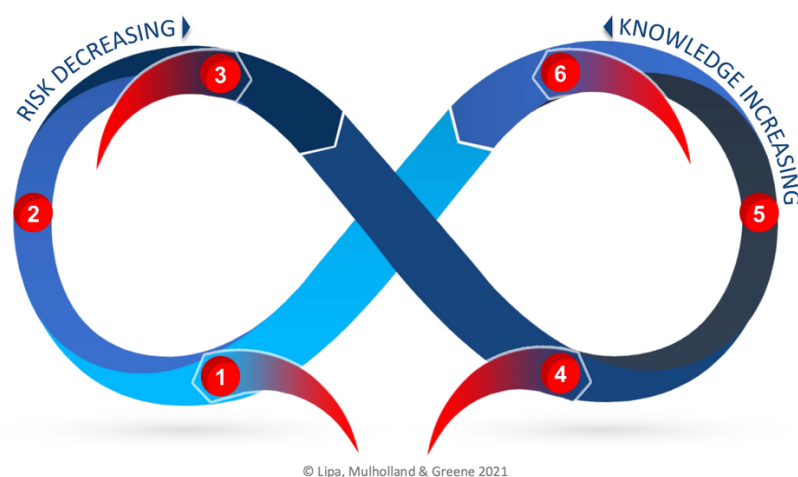


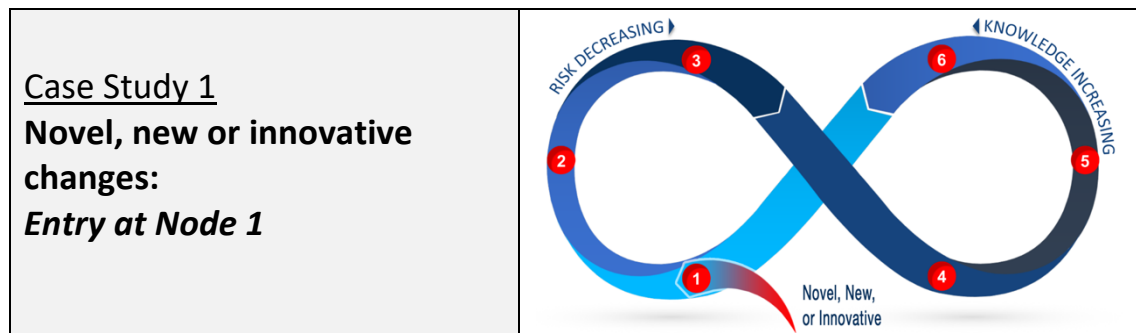
Figure 8-4 – Potential 'entry points' for the *RKI Cycle*

To demonstrate this, four change triggers were evaluated and their 'entry points' on the *RKI Cycle* are determined as follows:

- Novel, new or innovative changes: entry at node 1
- A risk control failure: entry at node 3
- Introducing a Disruptive or Transformational Technology: entry at node 4
- Continuous Improvement or Process Optimisation: entry at node 6

An example of each was reviewed via a case study, which is available in the referenced webinar (Lipa and Mulholland, 2021) and upcoming paper.

For the purpose of this thesis, the first case study which was for a *novel, new or innovative change*, is presented below.



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 organisation, 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*).

8.3 The *RKI Cycle* as a mechanism for data analytics to reduce risk (Example 3)

A third example of applying the *RKI Cycle* involves data analytics. This opportunity was realised when the researcher was invited to present at the launch of the *Guide to Data Analytics for Pharmaceutical Manufacturing* (PMTc, 2020) by the Pharmaceutical Manufacturing Technology Centre. The paper introducing the *RKI Cycle* (Lipa, O'Donnell and Greene, 2020a) is cited by this PMTC guide, and in preparing for the speaking engagement (Lipa, 2020b) the researcher reflected on the role the *RKI Cycle* could play as a mechanism for data analytics to *generate knowledge* and *enable risk reduction*. The PMTC guide acknowledges such a need, stating:

Data and data analytics are drivers for knowledge and knowledge generation, and can support KM and QRM systems, which should better inform risk management activities.

Furthermore, the PMTC guide states:

Data becomes knowledge through the vehicle of data analytics. Knowledge is a critical milestone that can be integrated and built upon to develop process understanding. Value is realised through such understanding.

This can be envisaged through a common representation linking data, information, and knowledge (Figure 8-5) as presented to PMTC (Lipa, 2020b). This figure, adapted from work by Rowley (Rowley, 2007) and Kane (Kane, 2018), represents the 'top' of the pyramid as *insight & understanding*, created starting from data and information contextualisation to create knowledge, and then from knowledge application through insight and understanding to support evidence-based decision making. Data analytics is a means of contextualisation of data.



Figure 8-5 – Data, Information, & Knowledge in support of evidence-based decision making

Relating this to the *RKI Cycle*, the focus of node 4 is to *acquire, grow, capture, and retain new knowledge*. It is here that new knowledge derived from data analytics should be injected into the cycle so that this knowledge becomes effectively managed and made visible and available via nodes 5 and 6 (Figure 8-6). This knowledge can then be applied to risk management via nodes 2 and 3 to support evidence-based decision making.

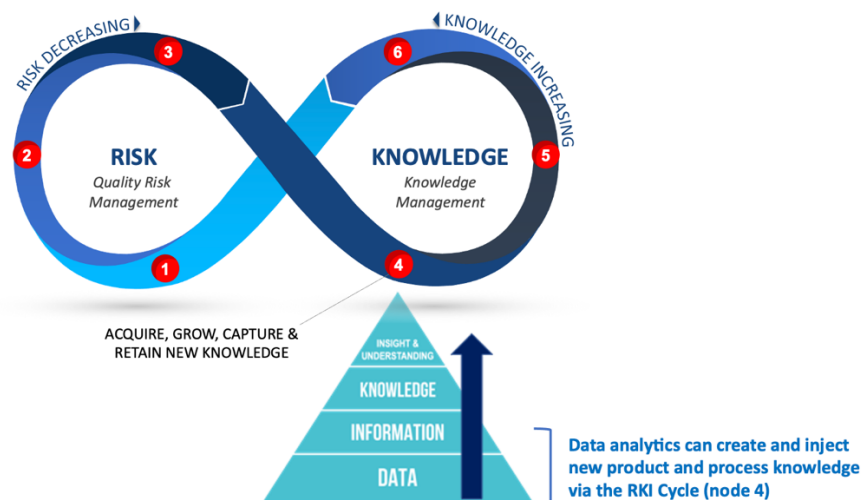


Figure 8-6 – Data analytics can inject new knowledge into the RKI Cycle

Further details linking data analytics, knowledge, and risk reduction are available in the presentation at the PMTC data analytics guide launch (Lipa, 2020b) and are discussed in Chapter 10.

While the pyramid shown in Figure 8-5 is often cited to descriptively relate *data*, *information*, and *knowledge*, this example application is about the ‘vertical integration’ of this pyramid (i.e., via data analytics to provide context to data and create knowledge), which has not been extensively studied. Further study on this is an opportunity highlighted in Chapter 12 of this thesis.

8.4 Summary – *RKI Cycle* application across the product lifecycle

As these examples illustrate, there are many potential applications where the *RKI Cycle* can be applied to relate and connect important activities throughout the PQS elements and across the product lifecycle. The researcher believes this is just the beginning of how the *RKI Cycle* can be used in this manner; the *RKI Cycle* has the opportunity to become a central, integrating framework with seminal impact for the industry and can lead to improved risk- and evidence-based decision making.

Chapter 9 follows describing an exploration into the concept of a *knowledge culture* as a means to define mindsets and behaviours for an organisation to excel in effectively managing knowledge across the lifecycle and further accelerate the impact of the *RKI Cycle*.

Chapter 9: *Knowledge Culture* as a Catalyst to Accelerate *RKI Cycle* Adoption and Impact

Having presented the *RKI Cycle*, with examples of its application across the product lifecycle, this final chapter in this part of the thesis explores a key factor: *knowledge culture*. Understanding and addressing the current organisational barriers to widespread KM adoption was an important factor in unlocking knowledge for use across the product lifecycle.

Organisational culture³² is a major barrier to change in many organisations. While there are many aspects to the culture of an organisation, this chapter focuses on exploring what a *knowledge culture* could be for the pharmaceutical industry. Industry-specific insights on the concepts of *quality culture* and cultural issues that act as barriers to KM are explored, including a view to understanding how they impact the *RKI Cycle*. A formative *knowledge culture* position for an organisation is proposed by the researcher with the intent of initiating dialogue and future research on the topic.

9.1 Attributes of quality culture

When developing a position of what a *knowledge culture* could look like for a pharmaceutical organisation, the researcher started first by exploring *quality culture* as a theme, as it has received significant attention in recent years. A 2014 survey by Corporate Executive Board (CEB), *Creating A Culture of Quality* (Srinivasan and Kurey, 2014), identified substantial savings opportunities for a company with a highly developed 'culture of quality' where an average savings of \$350 million per year could be gained as a result of not having to fix mistakes. The survey authors concluded that only four attributes need to be reviewed to actually predict a culture of quality: Leadership Emphasis, Message Credibility, Peer Involvement and Employee Ownership, as described in Table 9-1.

³² An organisation's culture consists of shared beliefs and values established by leaders and communicated and reinforced through various methods, ultimately shaping employee mindsets and behaviours for how to act. Organisational culture sets the context for everything an enterprise does (adapted (SHRM, 2021))

Table 9-1 – The four essentials of quality as per 2014 CEB Culture of Quality Survey (Srinivasan and Kurey, 2014)

Attribute	Description
Leadership Emphasis	Managers are told that quality is a leadership priority. Managers ‘walk the talk’ on quality. When evaluating employees, bosses emphasise the importance of quality.
Message Credibility	Messages are delivered by respected sources. Workers find that communications appeal to them personally. Messages are consistent and easy to understand.
Peer Involvement	Most employees have a strong network of peers for guidance. Peers routinely raise quality as a topic for team discussion. Like members of a sports team, peers hold one another accountable.
Employee Ownership	Workers clearly understand how quality fits with the job. Workers are empowered to make quality decisions. Workers are comfortable raising concerns about quality violations and challenging directives that detract from quality.

PDA published a Quality Culture Survey Report in 2015 (Patel *et al.*, 2015) and identified the top five attributes that can serve as surrogates for quality culture as:

- Management communication that quality is everyone’s responsibility
- Site has formal quality improvement objectives and targets
- Clear performance criteria for feedback and coaching
- Quality topics included in at least half of all-hands meetings
- Collecting error prevention metrics

PDA have aggregated these results and other content related to quality culture and launched a website dedicated to the topic, *PDA Quality Culture – PDA Resources for Developing a Mature Quality Culture* (PDA, no date).

ISPE published a Cultural Excellence Report in 2017 (ISPE, 2017) describing quality culture as follows (bold added for emphasis by the researcher):

*Quality culture is a feature of organisational design that fosters cross-functional ownership of quality. It treats quality not as a hindrance for success, but as a necessity that allows the company to make decisions that best benefit patients ...Quality culture refers to the **expressed and implied ways in which an***

organisation operates, affects quality performance and supply chain excellence, and ensures patient-focused outcomes.

From these three sets of insights (i.e., from CEB, PDA and ISPE), there appears no evident singular definition of quality culture, but clear themes emerge, including **visible leadership commitment**, the omnipresence of **quality outcomes in all actions**, the **active engagement of all staff**, and of the importance of related mindsets, attributes and cultural enablers.

9.2 Attributes of a culture effective in managing knowledge

To understand what a culture effective in managing knowledge could look like (i.e., a *knowledge culture*), the researcher also found it was helpful to start by understanding cultural issues that act as barriers to use and adoption of knowledge management and their impact to the *RKI Cycle*. Literature on barriers to KM was also reviewed.

9.2.1 Cultural attributes that act as barriers to KM in the pharmaceutical industry

The Knoco Survey on Knowledge Management 2020 (Knoco, 2020) included a question on barriers to KM. *Cultural issues* was one of eight choices given, and it ranked as the highest barrier to KM, with more votes for it than for *lack of prioritisation and support from leadership*, *lack of KM incentives*, *lack of KM roles and accountabilities*, *lack of defined KM approach*, and three additional barriers. Similarly, in the pharmaceutical industry-specific KM implementation survey published by ISPE in May 2020 (Kane *et al.*, 2020), *cultural issues* also ranked as the top barrier, tied with *lack of prioritisation and support from leadership*, from a list of the same potential barriers.

Both surveys went a step further and also asked a question on specifically *which* cultural issues have proven to be barriers from 10 provided choices. The choices of cultural issues as barriers were the same in both surveys. Table 9-2 created by the researcher summarises the top five cultural issues from each of the two surveys.

Table 9-2 – Top cultural issues as barriers to KM

Barrier Rank	Knoco Survey (Knoco, 2020)	ISPE Survey (Kane <i>et al.</i> , 2020)
1	Short term thinking*	Short term thinking*
2	Lack of openness to sharing*	Lack of performance drive
3	Secrecy	Lack of acceptance of new ideas
4	Lack of challenge to the status quo	Lack of honesty in sharing
5	Lack of empowerment	Lack of openness for sharing* (tie) Preferring invention to reuse (tie)

*Items in bold were identified as top 5 barriers in both surveys

Only the top five barriers were selected (of 10 total choices) to allow for simple prioritisation, and there was also an evident gap between the barrier five and the next highest-ranked barrier in both surveys, which supports this rationale. On review of the results, *short-term thinking* is a clear cultural issue, ranking as the top barrier in both surveys. *Lack of openness to sharing* is the other cultural issue that ranked in the top five of both surveys. Selecting these two barriers and for the purpose of this research, the additional barriers from the ISPE survey with its specific focus on the pharmaceutical industry, a prioritised list of six cultural issues facing KM in the pharmaceutical industry is proposed as follows:

- Short term thinking
- Lack of openness for sharing
- Lack of performance drive
- Lack of acceptance of new ideas
- Lack of honesty in sharing
- Preferring invention to reuse

Furthermore, the researcher in his professional experience has witnessed each of these cultural issues as barriers to KM; with this in mind, the next section explores the impact these six cultural issues can have on adopting the *RKI Cycle*.

9.2.2 The impact of cultural issues on the *RKI Cycle*

Considering the overarching goal of the *RKI Cycle* is to connect the disciplines of QRM and KM to ensure the best possible knowledge supports the best possible risk-based

decision, one can immediately see by mapping the six cultural issues onto the *RKI Cycle* how they can be barriers to supporting optimal QRM and KM (Figure 9-1).

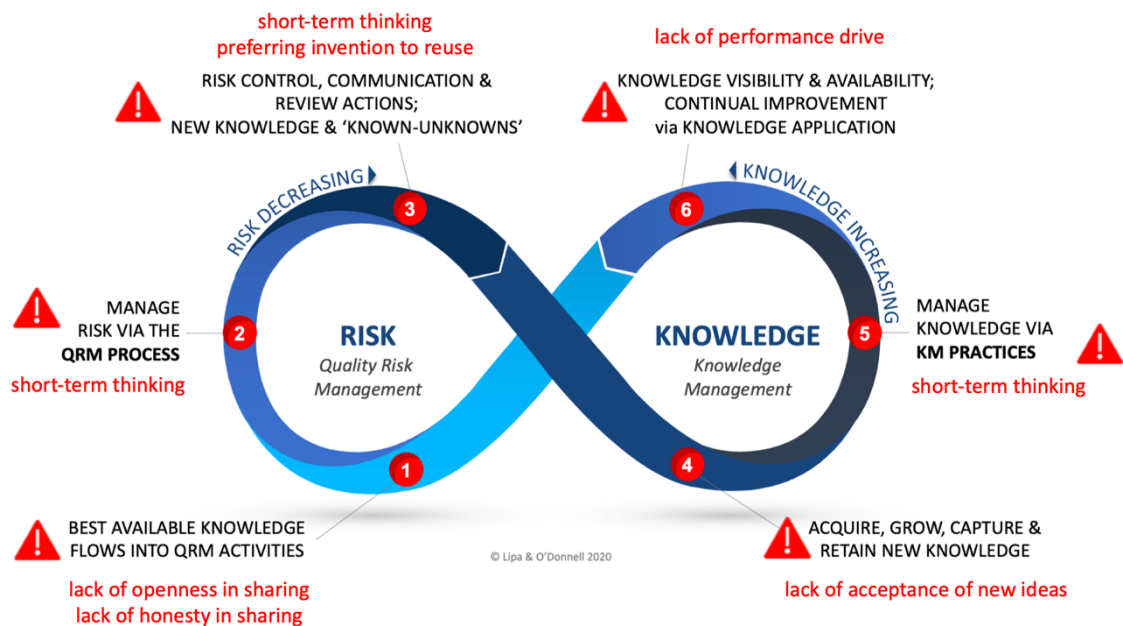


Figure 9-1 – Cultural issues as threats to the RKI Cycle (illustrative)

Although **each cultural issue is likely to impact multiple steps** of the *RKI Cycle*, Figure 9-1 highlights illustrative examples. For example, at *RKI Cycle* node 3, if *short-term thinking* is prevalent, knowledge associated with risks and through their risk assessments may not be captured optimally for future reuse. *Short-term thinking* has also been identified as a cultural barrier for effective KM (node 5) and can impact capturing sufficient context for future use during QRM (node 2). *Lack of a performance drive* will impact continual improvement at node 6. If there is *lack of openness or honesty in sharing*, the best available knowledge of the organisation certainly is *not* flowing into QRM activities (nodes 1 and 2).

These cultural issues almost certainly impact QRM and other processes as well. The culture of an organisation – which starts with values and manifests in mindsets and behaviours – is not confined to KM alone, but is rooted across many, if not all, processes within an organisation.

9.2.3 Cultural attributes that are supportive of KM in the pharmaceutical industry

When exploring cultural attributes that are supportive of KM, a literature review revealed insights into the meaning of a 'knowledge culture'. Oliver and Kandadi (Oliver and Reddy Kandadi, 2006) on a study of literature propose the following definition of knowledge culture:

A way of organisational life that enables and motivates people to create, share and utilise knowledge for the benefit and enduring success of the organisation.

Oliver and Kandadi then identified 10 factors which influenced the development of knowledge culture in large, distributed organisations as follows:

1. Leadership
2. Organisational structure (to include knowledge management roles (as opposed to knowledge management jobs))
3. Evangelisation (of the value of knowledge management activities to employees)
4. Communities of practice
5. Reward systems
6. Time allocation
7. Business processes (through embedding knowledge management in important knowledge intensive processes)
8. Recruitment (through consideration of knowledge sharing etiquette of potential employees)
9. Infrastructure (e.g., knowledge portals)
10. Physical attributes (e.g., office layout)

The researcher found the proposed definition insightful, although in the opinion of the researcher, the factors, while entirely valid, are more 'physical' or 'environmental' than behavioural-based. Milton and Lambe (Milton and Lambe, 2016) proposed a model consisting of 10 dimensions to an *organisational learning and knowledge management culture* summarised by the researcher in Table 9-3. Dimension 1 (supportive) is associated with learning culture and knowledge-valuing behaviours (e.g., **open**), and Dimension 2 (detracting) represents the antonym (e.g., *defensive*).

Table 9-3 – Organisational learning / Knowledge management culture dimensions (Milton and Lambe, 2016)

Dimension 1 (Supportive)	Dimension 2 (Detracting)	Definition (abridged)
Open	<i>Defensive</i>	The extent to which people feel comfortable having their performance (including mistakes) analysed for learning purposes.
Honest	<i>Dishonest</i>	The extent to which people will filter knowledge and information when communicating with peers or senior leaders; sometimes known as ‘transparency’.
Empowered	<i>Disempowered</i>	The extent to which people feel able to act on knowledge, independent of approval from their leaders.
Learner	<i>Knower</i>	The extent to which people put a value on acquiring new knowledge.
Need to share	<i>Need to know</i>	The extent to which people offer their knowledge to others rather than keeping it secret.
Challenge	<i>Acceptance</i>	The extent to which people seek to understand why things are the way they are; about intellectual curiosity and challenge the status quo.
Collaborative	<i>Competitive</i>	The extent to which people identify with and share in the success of others.
Remembering	<i>Forgetting</i>	The extent to which people acknowledge and incorporate the past when making plans for the future and the extent to which they consciously record decisions, judgments, knowledge, etc. for future reference.
Strategic patience	<i>Short-termism</i>	The extent to which people consider the ‘bigger picture’ and try to understand how their actions fit into the broader organisational vision.
Relentless pursuit of excellence	<i>Complacency</i>	The extent to which organisations acknowledge there is always room for improvement.

Finally, ISO 30401 *Knowledge management systems – Requirements* addresses knowledge management culture in Annex C (ISO, 2018) as follows:

Knowledge management culture is a supportive element of the organisational culture. A culture where the behaviours of seeking, sharing, developing and applying knowledge are encouraged and expected supports the establishment and application of the knowledge management system within the organisation. There is also a personal dimension to a knowledge management culture, where ultimately each individual has responsibility to demonstrate commitment through their own behaviour and interactions. A knowledge management culture acknowledges the value of individual and shared knowledge, as it benefits the organisation.

These insights were considered in the following section in the development of a proposed ideal *knowledge culture* for the pharmaceutical industry.

9.3 A proposed ideal 'knowledge culture' for the pharmaceutical industry

The researcher, having reflected on a philosophical dialogue with a senior leader responsible for pharmaceutical product commercialisation, proposed a knowledge culture must be engrained in an organisation much like that of a safety mindset: safety is everyone's responsibility, not just those who report into the safety organisation. The same analogy holds true for quality and should also be adopted for managing knowledge. **Ensuring safety in everything one does, building in quality, and managing knowledge are each ways of working, formed by how people think and act** (i.e., mindsets and behaviours) in the organisation, which is a key component of an organisational culture. Furthermore, these ways of working are not unique to safety, quality, or managing knowledge but can be synergistic with each other. For example, using KM processes to reflect after a safety incident or connecting quality risk management practitioners in a community of practice built on KM best practices. In the opinion of the researcher, it is the convergence of these ways of working where organisations can create clarity for their staff in how they are expected to act on a daily basis, rather than having distinct sets of behaviours across many topics (e.g., safety, quality, knowledge management, diversity & inclusion, operational excellence, etc.).

The researcher explored how the convergence of these ways of working could evolve by applying the insights gained in the previous sections, including the definition of *quality culture* (section 9.1), the top cultural issues facing knowledge management (section 9.2.1), the literature review on *knowledge culture* (section 9.2.3), and the researcher's professional experience. A formative definition of *knowledge culture* was proposed as follows:

A knowledge culture is one that demonstrates excellence in applying the best knowledge through an inherent bias to continuously reflect, learn, improve, share, grow, and transfer knowledge in order to positively affect quality performance, supply chain excellence, and ensure patient-focused outcomes.

This definition covers the *what* and the *why* of a knowledge culture. *How* such a knowledge culture might be achieved can also be benchmarked from the recurring themes in the definitions of quality culture, described through four attributes as follows:

- **Visible leadership commitment** to establish a vision, set expectations, and to create organisational alignment.
- **Managing knowledge as a way of working** is linked to the organisation's strategic objectives, delivering value in quality, operational benefits, and organisational and individual development opportunities.
- **Active engagement of all staff**, through application of organisational change management techniques.
- Well communicated **mindsets and behaviours** (as informed by the top cultural issues identified in section 9.2.1), reinforced by reward systems
 - Big picture thinking
 - Seeking and sharing 'by default'
 - Pursuit of excellence (including to pause, reflect and learn)
 - Embracing inclusion and innovation
 - Leading with transparency
 - Managing knowledge as an asset

An early illustration of this knowledge culture proposal is given below in Figure 9-2.

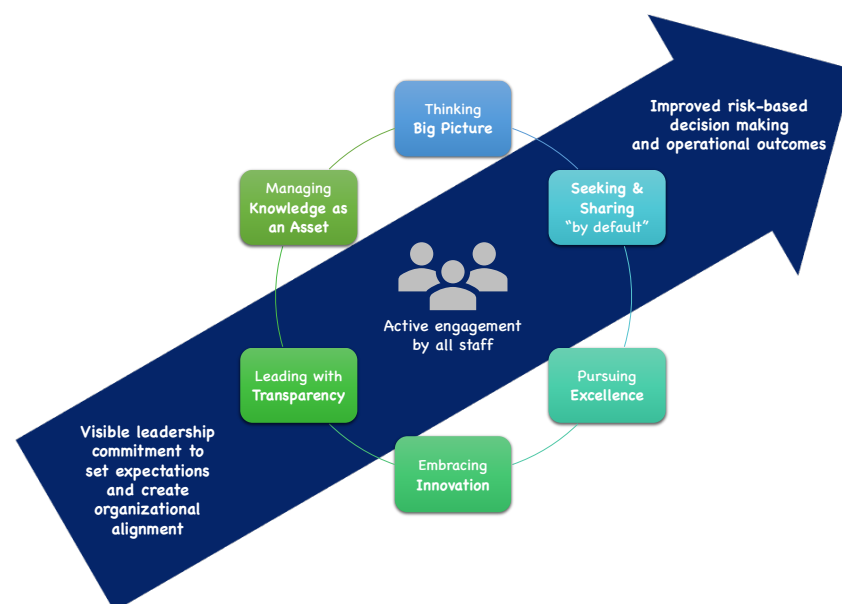


Figure 9-2 – The researcher's view on knowledge culture for the pharmaceutical industry

This proposal of a knowledge culture is preliminary in nature and is based on two key assumptions: the validity of the definition of a quality culture and the accuracy of the cultural barriers facing KM in the pharmaceutical industry. Further insight will be gained as the industry advances in quality culture and these learnings in what quality culture is and how it is achieved can inform the journey on knowledge culture. In regard to advancing the understanding of the cultural barriers to KM, this could be through additional data gathering (e.g., surveys) as well as feedback during application of the *RKI Cycle* and other outputs of this study.

Lastly and most importantly, any such knowledge culture needs to be adapted to fit the specifics of an organisation, including alignment with the mission of the organisation and consideration of the current organisational culture. Although well-suited for this study, this is certainly a topic which warrants further research.

9.4 Summary – A proposed ‘knowledge culture’ for the pharmaceutical industry

Imagine an organisation where such a knowledge culture exists and can bring to bear the power of the collective knowledge of the entire organisation to innovate, solve problems, and make the most informed risk-based decisions. Indeed, such a culture would be a catalyst for *RKI Cycle* adoption and acceleration of its impact. Patients, as stakeholders of the product produced by the industry should not expect any less, especially as they await innovative new therapies for unmet medical needs or face product availability issues for critical therapies they depend on.

Chapter 10 which follows provides a review of outputs, outcomes and impacts of this study.

Part Four: Outcomes and Impact, Conclusions, and Opportunities for Future Research

Part Four brings this research study thesis to a close by:

- Examining outputs, outcomes and impact (Chapter 10)
- A review of conclusions drawn from the research findings (Chapter 11)
- Presenting opportunities for future research (Chapter 12)

Chapter 10: Outputs, Outcomes, and Impacts of this Research Study

The purpose of this chapter is to describe the outputs, outcomes, and impacts of this research study (where applicable and known at the time of writing this thesis) as related by Figure 10-1 (UCD, no date).

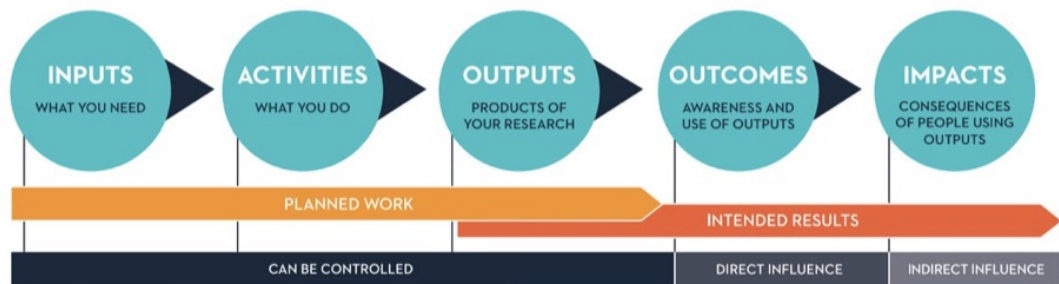


Figure 10-1 – The link between inputs and impacts (UCD, no date)

The approach at the outset of this study was to regularly consult and seek opinions and insights of various stakeholders across the pharmaceutical sector with the research activities to ensure the research was focused on problems that ultimately have an impact to the patient. This approach worked well for this study.

This study used a mixed methods approach and resulted in a series of outputs, the majority of which were disseminated in peer-reviewed papers and discussed in previous chapters of this thesis. These outputs include:

- *Knowledge Management Process Model* (Chapter 4)
- *RKI Cycle* (Chapter 5) and related contexts and concepts derived from this framework (e.g., *RKI Cycle as applied to ICH Q10*) (Chapter 5 and Chapter 8)
- *KT^E Framework* and *KT^E Toolkit* (Chapter 7), including the related outcomes of:
 - A current state assessment of knowledge transfer during technology transfer (Chapter 6)
 - Processes for tacit knowledge transfer (Chapter 7)
- Case studies for extending the *RKI Cycle* and mapping KM methods and tools across the product lifecycle (Chapter 8)

These outputs were disseminated in many fora through a variety of methods (e.g., papers, presentations, direct dialogue, formal/informal interviews, etc.) with sector stakeholders through an equally diverse set of channels (e.g., industry groups, advisory boards and committees, etc.), as illustrated in Figure 10-2.

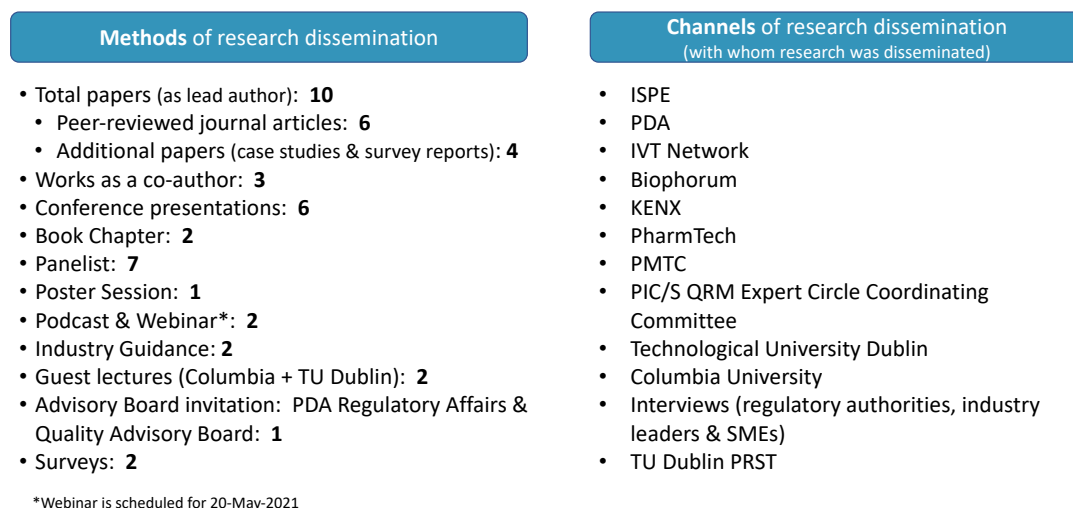


Figure 10-2 – Methods and channels of study dissemination

This approach has resulted in a high level of interaction with sector stakeholders on most every facet of this research study, allowing immediate *outcomes* and *impacts* of the study to be observed. Perhaps as a consequence of this approach, the research study and associated outputs have generated noteworthy media attention in recent months. The first example is from the EU-based *GMP Verlag Peither AG*, who publishes GMP news for the industry and featured the researcher’s 2021 PDA Annual Meeting presentation (Lipa, 2021a) in a feature titled *Innovations in Pharmaceutical Manufacturing* (Peither, 2021). This GMP Newsletter article featured only 4 of the 38 presentations given at the conference. The second and perhaps more significant media attention was that from International Pharmaceutical Quality (IPQ), entitled *Regulators Are Exploring with Industry How to Strengthen Quality Risk Management Practices, with Revision of ICH Q9 a Key Focal Point* (IPQ, 2021). One part of this article was entitled *Industry / Academia Research on QRM/KM Relationship* which featured several key outputs from this research study, including the *RKI Cycle* and *KT^E Framework*.

To demonstrate the significant outcomes and impacts, the researcher grouped them into five major themes, recognising the themes are not mutually exclusive and some overlap exists. Furthermore, any given output may affect more than one theme. These five themes are as follows:

1. A framework to address the untapped synergy between QRM and KM
2. Inaugural industry guidance on KM from a premier industry association
3. A comprehensive framework and toolkit for knowledge transfer during technology transfer, inclusive of tacit knowledge
4. A mechanism for data analytics to grow knowledge and reduce risk
5. Impact across the entire PQS

The outputs of the research grouped under these themes are discussed in the following sections of this thesis, with associated outcomes and impacts, as applicable and known.

10.1 Theme 1: A framework to address the untapped synergy between QRM and KM

Arguably the most exciting outcome of this research study is the progress on the relationship between QRM and KM, perhaps already of seminal importance given the preliminary response from stakeholders across the pharmaceutical sector. This focus on the QRM-KM intersection marked novel research for the industry in moving beyond the concepts presented in ICH Q10 to look more holistically across the regulatory guidance landscape at the relationship between *knowledge* and *risk*, and *knowledge management* and *risk management*. A key finding as explored in Chapter 5 was that there is near universal agreement that QRM and KM are highly interdependent yet there was broad agreement that they are only partially connected at best. This suggests there is an important gap to be filled to show how QRM and KM co-enable the PQS and lead to the best possible risk reduction for patients. In response to this, an output of this research is a framework, the *RKI Cycle* (Figure 5-6), which illustrates the relationship between risk and knowledge and demonstrates how QRM and KM are connected. As detailed in Chapter 8, outcomes of this framework are presented as examples and case studies which illustrate the broad applicability and importance of the *RKI Cycle* across the product lifecycle, and to the four elements of the PQS (e.g., change management,

etc.) proposed in ICH Q10 (ICH, 2008). The *RKI Cycle* was published in a peer-reviewed journal and was considered to be a significant contribution and of enough importance to potential stakeholders, that a regulator successfully petitioned the journal to allow open access to the paper to ensure broad global reach and dissemination. It was further made available openly with permission from the peer-reviewed journal through the TU Dublin *Level3* journal (Lipa, O'Donnell and Greene, 2020b).

This framework has been greeted with great interest and support across the pharmaceutical sector. One example of this is found in the results of a survey (Lipa, O'Donnell and Greene, 2021) to industry and regulators³³, summarised in the following points:

- When asked if the *RKI Cycle* was helpful as a means of depicting the relationship between QRM and KM **84% agreed the framework was helpful**, and only 9% disagreed.
- When asked “Would you support deploying such a framework within your organisation, in pursuit of better integration of QRM and KM?”, **92% of industry respondents answered Yes**, while 0% answered *No* (8% answered *Not sure*).
- When regulators were asked “Can you envisage companies deploying this framework within their organisations?” **83% of regulators answered Yes**, while 0% answered *No* (17% answered *Not sure*).
- When asked to identify and rank benefits (impacts) of improved QRM-KM integration, there was **acknowledgement that many important benefits could follow**. Table 10-1 lists the top five potential benefits of improved QRM-KM integration identified by each industry and regulator participants. The top two ranked items (in bold) were aligned across both sets of participants.

³³ The ‘regulator’ responses cited in the survey report represent the opinions of six members of the PIC/S QRM Expert Circle Coordinating Committee as of 21-February-2021, and do not represent the full view of the Coordinating Committee nor of the wider PIC/S organisation.

Table 10-1 – Top ranked potential benefits (impacts) of RKI Cycle

Rank	Top 5 Benefits (impacts) identified by industry participants	Top 5 Benefits (impacts) identified by regulator participants
1	Better risk-based decisions –where decisions are informed by risk and knowledge	Better risk-based decisions –where decisions are informed by risk and knowledge
2	More data/knowledge-driven risk assessments	More data/knowledge-driven risk assessments
3	Increased ability to leverage off of prior knowledge	Improved PQS effectiveness –where an integrated approach to risk and knowledge supports decision making, validation, change management, out-sourcing, etc.
4	Improved control strategies –which better reflect risk and knowledge	Improved protection and value for patients –reduced risks of defects, drug shortages, etc.
5	Improved PQS effectiveness –where an integrated approach to risk and knowledge supports decision making, validation, change management, out-sourcing, etc.	A better ability to deal with advances in manufacturing which utilise big-data, automation, artificial intelligence, etc.

- When asked about improvement opportunities of the *RKI Cycle*, the main suggestion was the interest in **more detail through examples, case studies, etc.**
- Open-ended feedback was solicited and was generally supportive, in alignment with the preceding highlights. Illustrative open-ended comments include:
 - *It is a simple and very useful graphic of the inverse relationship between risk and knowledge.*
 - *This Infinity loop is intuitive, easy to comprehend, and logical.*
 - *It visually clarifies the interdependency of both QRM and RM.*
 - *The linkage is [quite] clear to me. Knowledge informing risk and risk informing knowledge as a continuous process makes great sense.*
 - *KM is not well in practice today as compare to QRM could be a reason for just partial integration.*
 - *It explains very clearly how they are related and need to stay connected through long lifecycle in a constant state of learning and inertia.*
 - *Great work that will catalyse new thinking in this important area.*

Perhaps the most important impact will be the opportunity the *RKI Cycle* presents to improve QRM-KM integration. While the effort to apply the *RKI Cycle* has commenced and is discussed in Chapter 8, the researcher recommends additional stakeholder

guidance be developed to support implementation and move more quickly towards patients fully reaping the benefits of this important output.

In addition to the results of the survey, evidence of the *RKI Cycle's* immediate influence on industry stakeholders can be seen through interactions by the researcher with multiple industry associations as follows:

- The *RKI Cycle* is one of many outputs of this thesis featured in the *ISPE Good Practice Guide for Knowledge Management in the Pharmaceutical Industry* (ISPE, 2021b) as described in section 10.2. Furthermore, the *RKI Cycle* is featured as an element of the ISPE Guide cover artwork, which underscores the importance as viewed by industry KM SMEs authoring the ISPE Guide.
- The researcher presented several elements of this research study at the 2021 PDA Annual Meeting (Lipa, 2021a). This sparked significant interest from PDA, including a request to re-broadcast the recorded presentation to other geographic regions. Most notably, the PDA Regulatory Affairs and Quality Advisory Board (RAQAB) requested the researcher to attend the April 2021 board meeting to brief the board on the research and propose how PDA might advance the topic of KM for their membership. The researcher obliged, and provided a briefing (Lipa, 2021b). The main outcome of the PDA RAQAB meeting was that the board better understood KM and its criticality to QRM, and as a direct result of this briefing, PDA RAQAB is currently in the process of proposing a Task Force to develop a 'long range plan' for KM, of which the researcher has already been invited to participate (and possibly lead). A key deliverable of such a Task Force is likely to include a Technical Report on Knowledge Management (i.e., an additional industry guidance document).
- The *RKI Cycle* has also been cited by the recently published Pharmaceutical Manufacturing Technology Centre (PMTTC) Guide to Data Analytics for Pharmaceutical Manufacturing (PMTTC, 2020), given its relevance to translating

information from data analytics into knowledge and applying this knowledge to reduce risk.

A final point of relevance for the *RKI Cycle* was made by Dr. Edward Hoffman, retired Chief Knowledge Officer from NASA. Dr. Hoffman participated in the Confirmation Examination for the researcher in November 2020. During the discussion following the confirmation exam, Dr. Hoffman provided supportive feedback for this model and acknowledgement of the underlying challenges in connecting risk management and knowledge management based on his experiences at NASA. Dr. Hoffman remarked:

I love the model – I love the connection between risk and knowledge. I’ve always seen it. It’s essential. For 20 years I’ve been stunned by the lack of connection between QRM and knowledge, and partly is that there are so many silos in organisations.

These insights by Dr. Hoffman were important as they verified the fundamental underlying assumption of the importance of connecting risk and knowledge, and furthermore that Dr. Hoffman had witnessed similar challenges in another highly technical and complex industry.

The strong interest, supportive feedback, and potential for significant impact of the *RKI Cycle* appears evident through these early reactions across the sector stakeholders, even though the *RKI Cycle* was published barely six months prior to the submission of this thesis. The researcher is delighted with this response and the dialogue it has created within the sector. Future work is planned and will be discussed in Chapter 12.

10.2 Theme 2: Inaugural pharmaceutical industry guidance on KM from a premier industry association

Perhaps the most visible, tangible, and immediate outcome of this research is the inclusion of significant elements of it in an upcoming pharmaceutical industry guidance document on knowledge management from a premier industry association, ISPE. ISPE ‘is the world’s largest not-for-profit association serving its members by leading scientific, technical, and regulatory advancement through the entire pharmaceutical

lifecycle’ (ISPE, 2021a). ISPE has over 18,000 members in 90 countries (ISPE, 2021c) and produces industry guidance documents as characterised by the ISPE website (ISPE, 2021d):

Produced by pharmaceutical manufacturing industry professionals, ISPE Guidance Documents provide the practical, "real world" information you need to help your company build on current best practices to meet and exceed regulatory standards...Reflecting current regulatory expectations and best practices, Good Practice Guides (GPGs) help to narrow interpretation of regulatory standards for improved compliance and quality, efficiency, and cost reductions. They typically focus on the "how".

These guidance documents are created through a robust process including authorship by a team of SMEs, industry review and feedback, and internal ISPE processes for quality control. This new guidance document, *ISPE Good Practice Guide, Knowledge Management in the Pharmaceutical Industry*, was published in May 2021 (ISPE, 2021b). As mentioned in Chapter 4 (section 4.1,) the researcher was a member of the team of SME authors of this ISPE Guide on KM, comprised of 10 industry SMEs on knowledge management.

While the overall guide itself was not a direct output of this research, this research study significantly informed and shaped the ISPE Guide and was instrumental in addressing industry feedback. In particular, the *Knowledge Management Process Model*, an output of this research introduced in Chapter 4 of this thesis (Figure 4-2), plays a central role in the ISPE Guide and is featured as a standalone chapter in the Guide (Chapter 4). Consistent with the intent of the ISPE Guide, this *Knowledge Management Process Model* provides a previously missing ‘how’ to facilitate understanding and application of KM. In all, a total of seven outputs from this research study are featured in the ISPE Guide, as listed in Table 10-2.

Table 10-2 – Thesis outputs used by ISPE Good Practice Guide: Knowledge Management

ISPE Guide Reference	Reference to output from this thesis
Figure 2.3 Section 2.1.3	Figure 5-5 – Decreasing risk though increasing applied knowledge over time
Figure 4.1 Section 4.1	Figure 4-2 – Knowledge Management Process Model
Figure 5.4 Section 5.2.2	Figure 6-2 – Challenges associated with technology transfer knowledge transfer
Figure 5.1 Section 5.2.6	Table 8-1 – Stage-appropriate KM methods & tools across the product lifecycle
Figure 11.1 Appendix 5	Figure 5-6 – The Risk-Knowledge Infinity Cycle applied to ICH Q10
Figure 14.1 Appendix 8	Figure 7-1 – The KT ^E Framework on a page *
Figure 14.2 Appendix 8	Figure 7-2 – Technology Transfer Batch Execution Review

*A simplified version was used in the ISPE Guide, this version is available in the PDA article (Lipa, Greene and Calnan, 2021)

Throughout the development of the Guide, it was not the researcher’s intention to self-advocate or ‘market’ use of these outputs. Rather, as some on the ISPE SME author team were aware of the ongoing research effort and research progress was being regularly published, these inclusions were typically a ‘pull’ from the ISPE SME author team members and were subsequently vetted through the full ISPE SME author team and industry review processes³⁴. During the review process, 258 comments were received from 27 pharmaceutical industry and health authority representatives and addressed by the SME author team.

These outputs used by the ISPE Guide cover a broad scope from this thesis, lending further credibility and visible endorsement of this research study. The publishing of the ISPE Guide will immediately make these outputs broadly visible and available to the industry where its impact will become apparent over time.

³⁴ ISPE Guides go through a robust guidance document process involving pharmaceutical industry professionals. The Guides are authored by pharmaceutical industry representatives and subject matter experts (SMEs). Once authored, Guides are reviewed and approved by pharmaceutical industry representatives in the same subject matter but not the group who authored the Guide. (ISPE, 2021d)

10.3 Theme 3: The first comprehensive framework and toolkit for knowledge transfer during technology transfer, inclusive of tacit knowledge

This research study started with an initial focus on improving knowledge transfer during technology transfer, in particular of tacit knowledge transfer, and one of the first outputs of the research was a framework for enhanced knowledge transfer, the *KT^E Framework*. The research study started with the characterisation of the current state of knowledge transfer during technology transfer. The results of this assessment, published in a peer-reviewed paper (Lipa, Kane and Greene, 2019), verified that there is little guidance for knowledge transfer overall, and almost none for tacit knowledge (inclusive of 'know-how'), leading to explicit knowledge transfer being only *marginally effective*, and tacit knowledge as being *somewhat ineffective*. This paper subsequently received recognition as the *IVT 2020 Author of the Year Award* (IVT Network, 2020), a testament to the interest in and relevance of the topic.

The subsequent development of the *KT^E Framework* (Figure 7-1), as detailed in Chapter 7, led to several meaningful interactions with stakeholders, including feedback sessions with several pharmaceutical companies and a presentation at the *2020 PDA Europe Quality & Regulations Conference* (Lipa, 2020a) where the research insights on technology transfer and knowledge transfer were shared. This presentation was well received and triggered a request by the PDA SME team authoring a revision to *PDA Technical Report No. 65, Technology Transfer* (PDA, 2014b) to solicit input for the PDA Technical Report from the researcher on knowledge transfer. The revision of this PDA Technical Report was being planned in 2019 and was a subject of the researcher's critique during the literature review, as detailed in Chapter 2 (section 2.3.2). The researcher used this opportunity to influence the revision to the PDA Technical Report, providing several comments for consideration, with a focus on improving knowledge transfer and the recognition of tacit knowledge. This PDA Technical Report is still in revision as of the date of this thesis, so the extent to which these comments are incorporated is not yet known.

Also related to knowledge transfer and of great interest to the researcher is the subtopic of tacit knowledge transfer. To this end another output of the study was the design and

deployment by the researcher of new KM practices to focus on tacit knowledge transfer as discussed in Chapter 7 (section 7.2) of this thesis. The results – captured as a case study (Lipa, Kane and Greene, 2020) – are promising as they are shown to drive proactive interventions and a significant reduction in deviations in the quality system for the company involved in the case study. The impact of this was **an immediate and direct reduction of risk and improvement in right-first-time qualification batch execution**. This in turn benefited patients as this vaccine product was designated a *breakthrough therapy*³⁵ by the FDA, and successful on-time qualification meant patients would have access to an important new therapy more quickly. Furthermore, there were benefits to the company in the form of meeting cost and schedule commitments (as well as avoiding reputational risk if delays were encountered).

Lastly, a late-breaking development for this research study is an unsolicited case study of *KT^E Framework* application. Upon reading the peer-reviewed article in the *PDA Journal of Science and Technology* in which the *KT^E Framework* was published (Lipa, Greene and Calnan, 2021), a team from a Singapore manufacturing facility who had previously been a receiving unit in a technology transfer created a matrix³⁶ based on their challenging experience with a technology transfer as shown in Figure 10-3.

³⁵ *Breakthrough Therapy* designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). (<https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy>)

³⁶ The matrix in the figure has been anonymised to blind the identity of the organisation and the associated product.

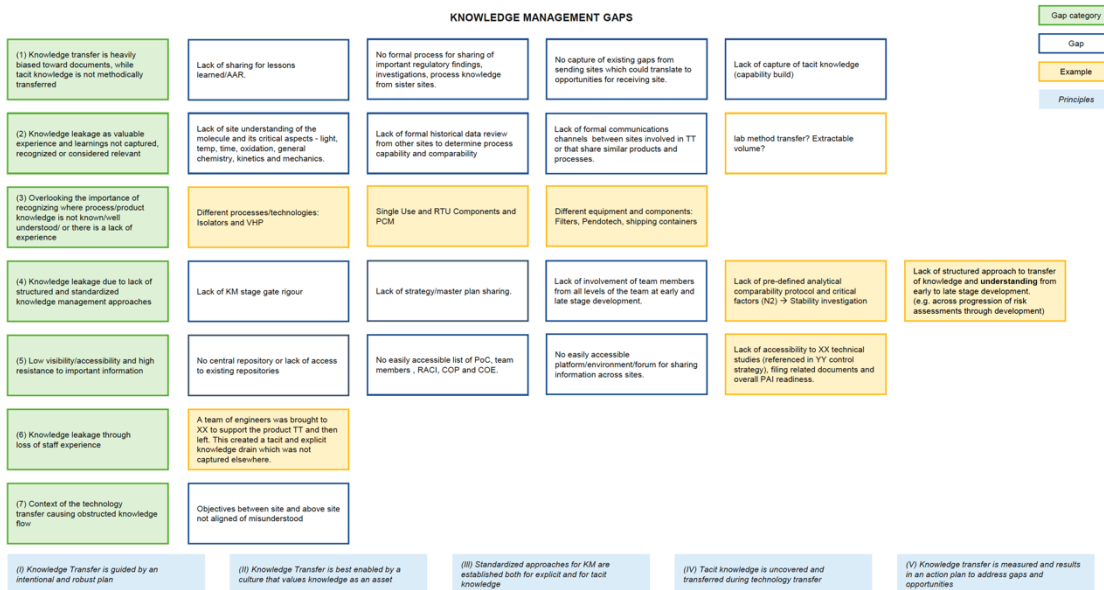


Figure 10-3 – A gap assessment against the KT^E Framework (case study)

The green boxes in Figure 10-3 ('Gap Category' as per included legend) depict the knowledge transfer challenges identified by the researcher (e.g., *knowledge leakage*, as detailed in Chapter 6, section 6.2.1). The blue boxes in Figure 10-3 ('Principles' as per included legend) depict the high-level requirements identified by the researcher (e.g., *KT is guided by an intentional and robust plan*, as detailed in Chapter 6, section 6.2.2). Figure 10-4 highlights these linkages (in green and blue boxes respectively), mapped back to the detailed requirements for a knowledge transfer framework as defined in Chapter 6 (section 6.2.2), Figure 6-3.

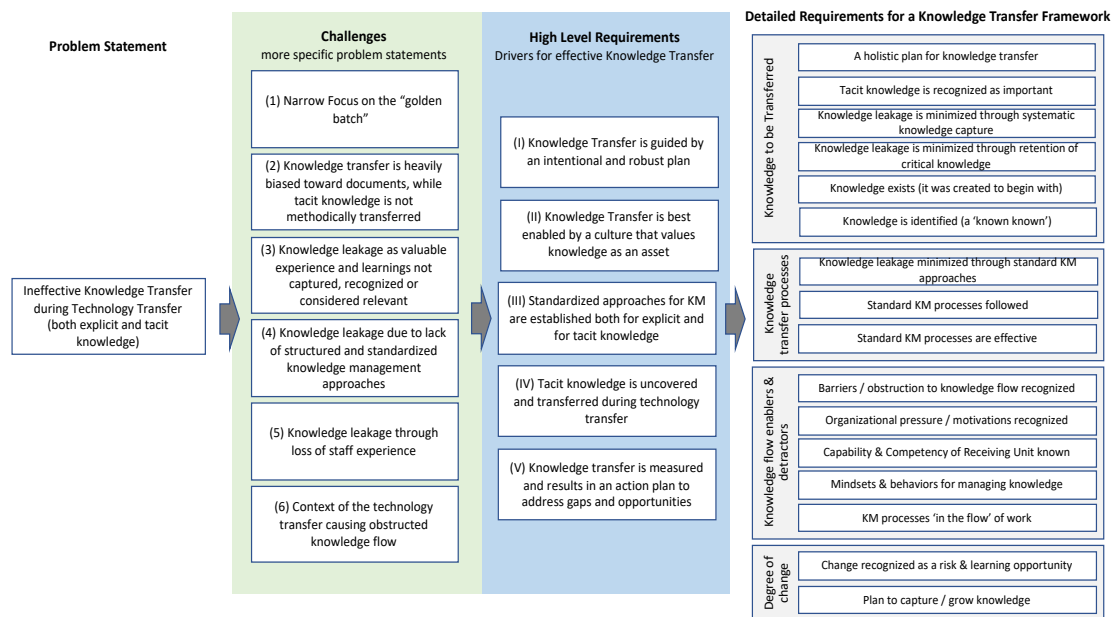


Figure 10-4 – Mapping of KT^E Framework case study to knowledge transfer framework requirements

The Singapore manufacturing site contacted the researcher directly, as the researcher was the corresponding author with contact details listed on the published paper. As the KT^E Framework was published only two months prior to this contact, this is clear evidence of the research having an immediate, direct, and global impact on how people view knowledge transfer during technology transfer. This is especially true as this case study identified clear issues which demonstrate the need for why the framework was created. The team in Singapore indicated to the researcher that they plan to develop a knowledge management playbook for technology transfer based on the KT^E Toolkit, aligned with the researcher's intended use.

As these examples demonstrate, the KT^E Framework and associated KT^E Toolkit as outputs from this research study have already demonstrated tangible outcomes and impact, including:

- Increased awareness of the current issues with knowledge transfer and its effectiveness, including looking at technology transfer through a knowledge transfer lens
- Improvements in quality and right-first-time outcomes through new tacit knowledge-focused KM practices

- Influence on an additional industry guidance document (PDA Technical Report No. 65, Technology Transfer (PDA, 2014b))

10.4 Theme 4: A mechanism for data analytics to grow knowledge and reduce risk

Preliminary research into the link between data analytics and KM marks another area of novelty in this research study. As described in Chapter 8 (section 8.3), the *RKI Cycle* can act as a mechanism to connect data analytics to risk reduction. Currently the topic of linking data analytics (a topic receiving significant attention recently due to the focus on digital transformations in industry (CIO, 2018)), to KM and to QRM has not been well defined.

The PMTC Guide to Data Analytics for Pharmaceutical Manufacturing (PMTC, 2020) states:

data & analytics are central to informing quality systems ... Data and data analytics are drivers for knowledge and knowledge generation, and can support KM and QRM systems, which should better inform risk management activities.

The description for Figure 6.1 from the PMTC Guide (PMTC, 2020) (Item A in Figure 10-5) includes:

[Figure 6.1] highlights the quality systems and regulatory guidelines that enable a state of control to be maintained during the product manufacturing lifecycle ... the figure shows data and data analytics as central to informing these quality systems, which can provide even greater opportunity to ensure the safety of the public health and patients.

The researcher, during his presentation at the launch of the PMTC Guide launch (Lipa, 2020b), demonstrated how the *RKI Cycle* can provide the missing mechanism for the 'how' to connect data and data analytics to KM and QRM to achieve these outcomes (Item B in Figure 10-5).

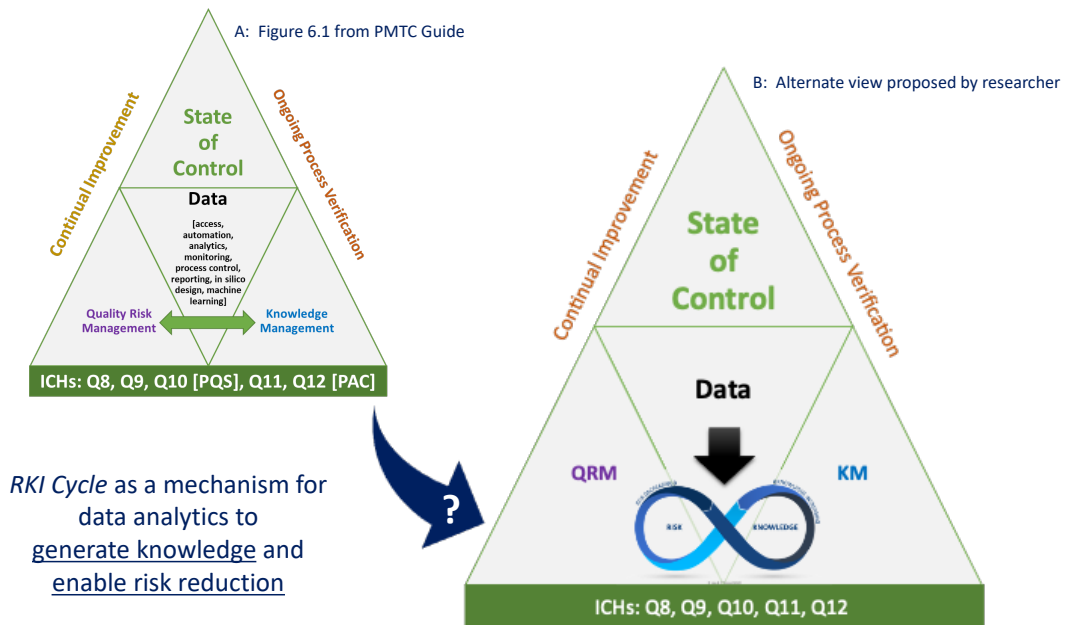
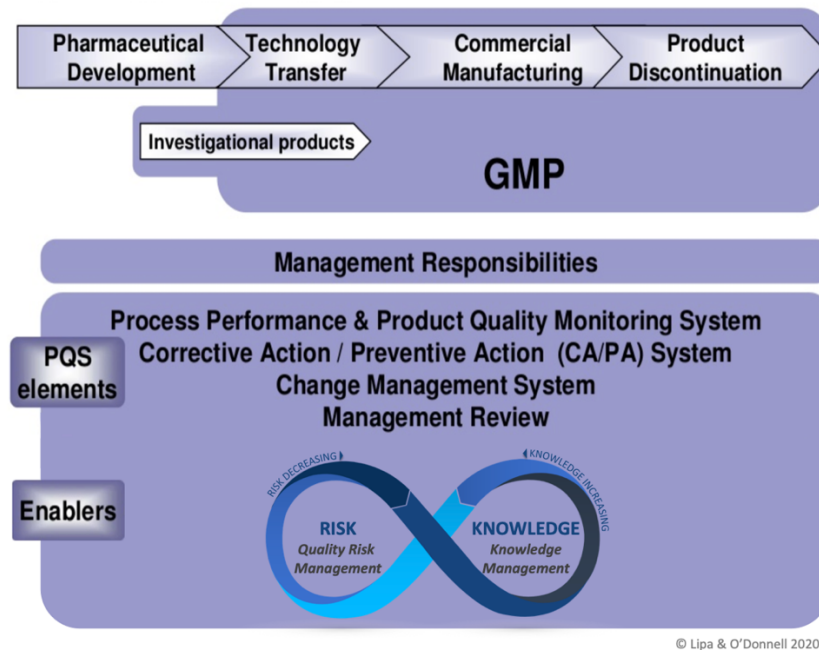


Figure 10-5 – RKI Cycle as a mechanism for data analytics to inform KM and QRM

These concepts were well received and have initiated dialogue with PMTC for future cross-discipline research and connectivity. This is an important topic for future research as will be presented in Chapter 12, which can also help further clarify the relationships between data, information, and knowledge.

10.5 Theme 5: Impact across the entire Pharmaceutical Quality System

Another major outcome of this research study is the potential for broad application across the PQS, ‘top to bottom’ (i.e., across all PQS enablers and elements) and ‘end to end’ (i.e., across all PQS lifecycle stages). Although this study started with a focus on technology transfer, it has reshaped the understanding of KM as a PQS enabler, engaged the practice of QRM to truly co-enable the PQS, proven the impact of improved knowledge management and knowledge transfer to the lifecycle stage of technology transfer, and has been mapped to demonstrate how many of these outcomes can extend to impact the entire product lifecycle. Figure 10-6 captures the essence of this concept, where KM and QRM are interconnected to each other, directly to the PQS elements and applicable across the product lifecycle.



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Figure 10-6 – A re-framed and united PQS foundation

This holds exciting promise for the reach and significance of the *RKI Cycle*, warranting further research and further development of support materials (e.g., a training and application package).

10.6 Summary of research study outputs, outcomes, and impacts

Table 10-3 provides a summary of the five research impact themes with associated mapping of outputs, outcomes, and impacts, as defined in Figure 10-1 at the start of this chapter. Note that several of the outputs (e.g., *RKI Cycle*) apply to more than one impact theme, as these outputs are not mutually exclusive to any single outcome or impact.

Table 10-3 – Mapping impact themes to outputs, outcomes, and impacts

Impact Theme	Outputs Products of research	Outcomes Awareness and use of outputs	Impacts Consequences of people using outputs (*planned / future)
1: A framework to address the untapped synergy between QRM and KM	<ul style="list-style-type: none"> • Various publications & presentations • Report: QRM-KM current state integration • Framework: <i>RKI Cycle</i> 	<ul style="list-style-type: none"> • Recognition within pharma sector that QRM & KM should be well connected but are not in practice • <i>RKI Cycle</i> verified beneficial, made publicly available • ISPE Good Practice Guide: Knowledge Management • PMTC Guide to Data Analytics for Pharmaceutical Manufacturing • PDA RAQAB evaluating a Task Force for KM • Media coverage by IPQ and GMP Verlag Peither AG 	<ul style="list-style-type: none"> • Better risk-based decisions* • Improved control strategies* • Improved PQS effectiveness* • Improved protection and value for patients (e.g., reduced risks of defects, drug shortages)* • A better ability to deal with advances in manufacturing which utilise big-data, automation, artificial intelligence, etc.*
2: Inaugural industry guidance on KM from a premier industry association	<ul style="list-style-type: none"> • Various publications & presentations • Model: <i>Knowledge Management Process Model</i> • Framework: <i>RKI Cycle</i> • Framework: <i>KT^E Framework</i> • Case study: <i>Tacit knowledge transfer</i> 	<ul style="list-style-type: none"> • ISPE Good Practice Guide: Knowledge Management 	<ul style="list-style-type: none"> • Better risk-based decisions, leading to improved patient value and safety* • Operational outcomes for organisations managing knowledge as an asset (cost savings, time savings, reduced risk, improved right-first-time execution, more competent workforce)*
3: The first comprehensive framework and toolkit for knowledge transfer during technology transfer, inclusive of tacit knowledge	<ul style="list-style-type: none"> • Various publications & presentations • Current state assessment: <i>Technology transfer KT effectiveness</i> • Framework: <i>KT^E Framework</i> • Toolkit: <i>KT^E Toolkit</i> • Processes: <i>Tacit knowledge transfer</i> • Case Study: <i>Tacit knowledge transfer</i> 	<ul style="list-style-type: none"> • Increased recognition of poor knowledge transfer • ISPE Good Practice Guide: Knowledge Management • Case study: <i>Tacit knowledge transfer</i> • Case study: <i>KT^E Framework gap assessment</i> • Further consideration of KM for PDA Technical Report No. 65, Technology Transfer • Media coverage: IVT Author of the Year Award 	<ul style="list-style-type: none"> • Improved outcomes of technology transfer, including reduction of risk and fewer quality defects • Knowledge available during commercial manufacturing to support KM and QRM (e.g., better risk-based decisions and operational outcomes)*
4: A mechanism for data analytics to grow knowledge & reduce risk	<ul style="list-style-type: none"> • Various publications & presentations • Framework: <i>RKI Cycle</i> 	<ul style="list-style-type: none"> • Recognition as an area of future study with PMTC, with post-graduate research opportunities being explored 	<ul style="list-style-type: none"> • To be determined, but ultimately reducing risk through ensuring data analytics-driven insights are recognised as knowledge and made available through KM
5: Impact across the entire Pharmaceutical Quality System	<ul style="list-style-type: none"> • Various publications & presentations • Framework: <i>RKI Cycle</i> 	<ul style="list-style-type: none"> • Recognition of the broad applicability and centrality of the <i>RKI Cycle</i> to the PQS and opportunities to further develop <i>RKI Cycle</i> application packages 	<ul style="list-style-type: none"> • To be determined, but ultimately scaling impacts above across lifecycle for greater impact

There are likely additional outcomes and impacts to emerge from this research study, perhaps including:

- Further application of the *RKI Cycle*, both across the lifecycle but also to other types of risk beyond quality risk, as the underlying relationship between knowledge and risk is not unique to quality. The concepts of the *RKI Cycle* are broadly applicable to other types of risk, such as technical risk, supply chain risk, and financial risk.
- The creation of additional KM frameworks for other stages of the product lifecycle, based on the principles defined in the *KT^E Framework*.
- The global pharmaceutical supply chain may be reshaped in the wake of the COVID-19 pandemic, in response to ‘re-shoring’ efforts driven by supply chain security concerns. This in turn could lead to a tidal wave of technology transfers, for which the *KT^E Framework* could see accelerated uptake and relevance.
- Subsequent refinement of the concept of knowledge culture for the pharmaceutical industry.
- A notable approach to this research study is the *systems thinking*³⁷ applied by the researcher, including focus on previously unstudied intersections between these related but distinct disciplines of KM, QRM, quality culture, and data analytics. As such, this research study has also reached a diverse audience given the nature of this research and identified many opportunities for future research, as will be explored in Chapter 12.

The researcher believes this research study has broad **reach**, as it has the potential to affect many in the pharmaceutical sector in how to manage knowledge to reduce risk and improve operational performance. The research study outcomes are arguably **significant** since they have the opportunity to have a favourable impact on patient protection, as well as the already proven impact to increase quality and right-first-time

³⁷ Systems thinking as defined by Arnold and Wade is “a set of synergistic analytic skills used to improve the capability of identifying and understanding systems, predicting their behaviours, and devising modifications to them in order to produce desired effects.” (Arnold and Wade, 2015)

execution during technology transfer. Furthermore, the researcher believes this study has 'planted many seeds to germinate' which will grow over the months and years ahead and deliver yet unknown outcomes and impacts.

The following chapter presents a conclusion to this research study and includes a summary of the primary outputs mapped back to the relevant areas of the PQS to which they relate.

Chapter 11: Conclusions to this Research Study

The purpose of this chapter is to draw final conclusions for this research study.

As stated in Chapter 1 (section 1.1), the **overarching goal of this research study was to provide tangible benefit to the patient by improving PQS effectiveness through meaningful advancement of KM as a PQS enabler**. Stated simply, improving KM will improve the PQS effectiveness and corresponding product quality, and in turn providing important benefits to patients.

On reflection of the research activities and outputs described in this thesis and as a means to summarise the research progression, the researcher created Figure 11-1 to illustrate the **research study context** as the starting point of this research and a **roadmap** of this research study. The study roadmap illustrates the cascading requirements for the dual PQS enablers of QRM and KM. Furthermore, the study roadmap includes the starting point for several levels of KM and its connectivity to QRM (**FROM: ... with red text**) and defines what is now possible (**TO: ...**) as a result of the contributions of this study.

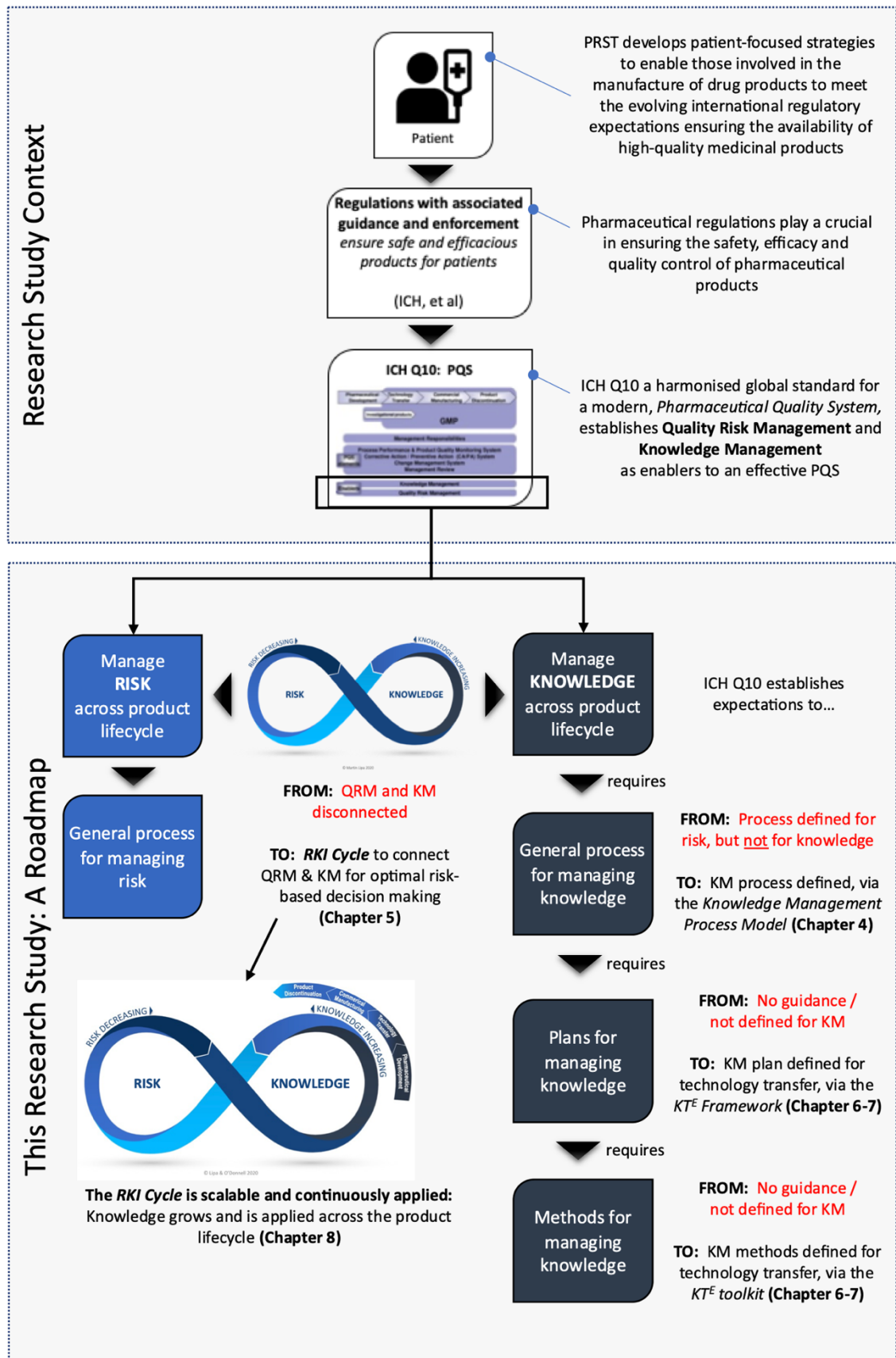


Figure 11-1 – A roadmap of this research study

The introduction of ICH Q10 positions an effective PQS as a means to enhance the quality and availability of medicines in the interest of public health:

ICH Q10 demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

As introduced in Chapter 1 (section 1.6) and explored throughout this research study, these research outputs have the opportunity to impact several areas of the PQS as first presented in Figure 1-6:

1. KM as an enabler to the PQS, via a *Knowledge Management Process Model*
2. KM with QRM as dual enablers to the PQS, via the *RKI Cycle*
3. Technology Transfer as a stage in the product lifecycle via the *KT^E Framework*
4. The end-to-end product lifecycle, via broad application of the *RKI Cycle*

Figure 11-2 was created by the researcher to illustrate where primary research study outputs map to the various areas of the PQS.

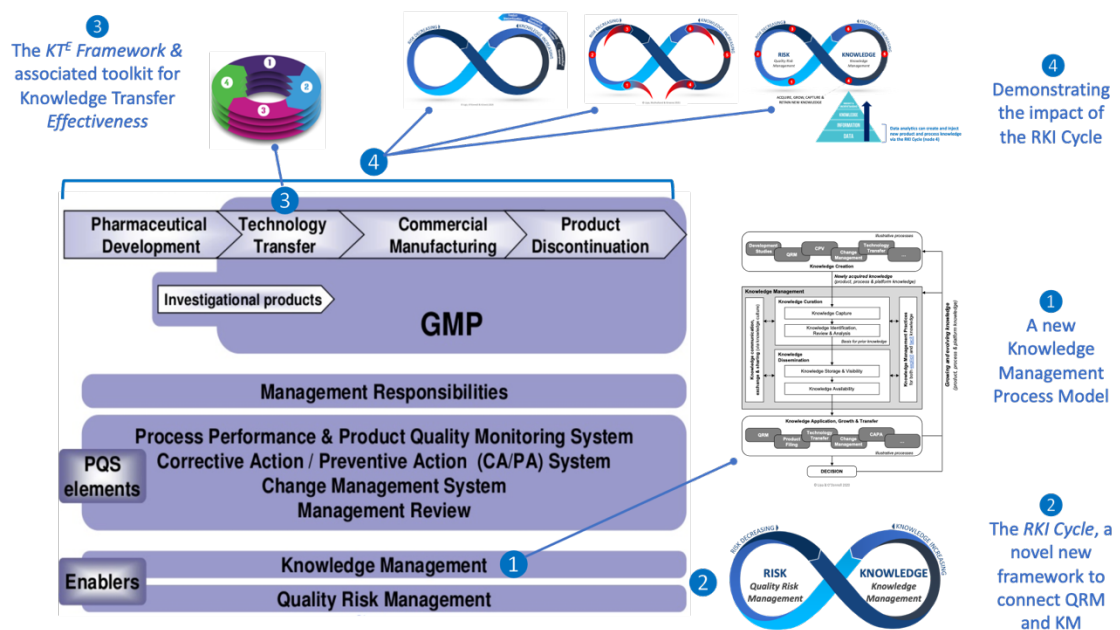


Figure 11-2 – Mapping of selected research study outputs to the PQS

The impact of each of these research outputs to the PQS is summarised as follows:

1. The new *Knowledge Management Process Model*, as presented in Chapter 4 and designed based on the QRM Process Model from ICH Q9, can broadly impact how KM is understood as an enabler to the PQS, through a more pragmatic, structured, and sequential breakdown of the KM process. This new *Knowledge Management Process Model* addresses the definition KM provided by ICH Q10, and goes further to include the concepts of tacit knowledge, the connection of KM to business processes, and enablers to successful KM (e.g., standardised processes and sponsorship). Through a better understanding of the mechanics of KM, the industry can better utilise KM to enable all facets of the PQS and beyond for operational effectiveness, employee engagement, and more.
2. The *Risk-Knowledge Infinity Cycle*, or *RKI Cycle*, a novel framework to connect QRM and KM as presented in Chapter 5, can (and has already started to) define the understanding of the relationship between risk and knowledge, the relationship between risk management and knowledge management, and the importance of linking the two. Linking these two disciplines offers the promise of improving fundamental PQS outcomes, including better risk-based decision making, more data and knowledge driven risk assessments, better use of prior knowledge and improved protection and value for patients, to name a few. This framework links QRM and KM and has a resulting impact on **every facet** of the PQS.
3. The *KT^E Framework* and *KT^E Toolkit* to enhance knowledge transfer effectiveness (Chapter 7) are specifically designed as a knowledge management approach for the lifecycle stage of technology transfer and have proven their effectiveness to technology transfer. The underlying principles to this framework and toolkit have the potential to be rapidly scaled across the product lifecycle.
4. The *RKI Cycle* has broad applicability *across the end-to-end product lifecycle*, as explored in Chapter 8, as well as the potential to be a uniting mechanism for

QRM, KM, and data analytics, ensuring the best possible risk-based decisions are made across the product lifecycle, whether for product development, technology transfer, change management, or any other element (or lifecycle stage) of the PQS.

The preliminary outcomes and impact of each one of these research outputs are described in detail in Chapter 10 of this research study through a set of themes intended to convey tangible and meaningful advancements. Collectively, these outcomes make a substantial contribution to the PQS, with significant impact and broad reach.

As introduced in Chapter 1, the aim of this research study was to benefit the patient by improving the effectiveness of the PQS (Figure 1-1). In reflecting on this goal, with the study outputs and their impact to PQS effectiveness well characterised, the researcher created Figure 11-3 (based on Figure 1-1 and Figure 11-2) as a means to ‘close the loop’ back to the patient by illustrating how these outputs lead to patient benefits.

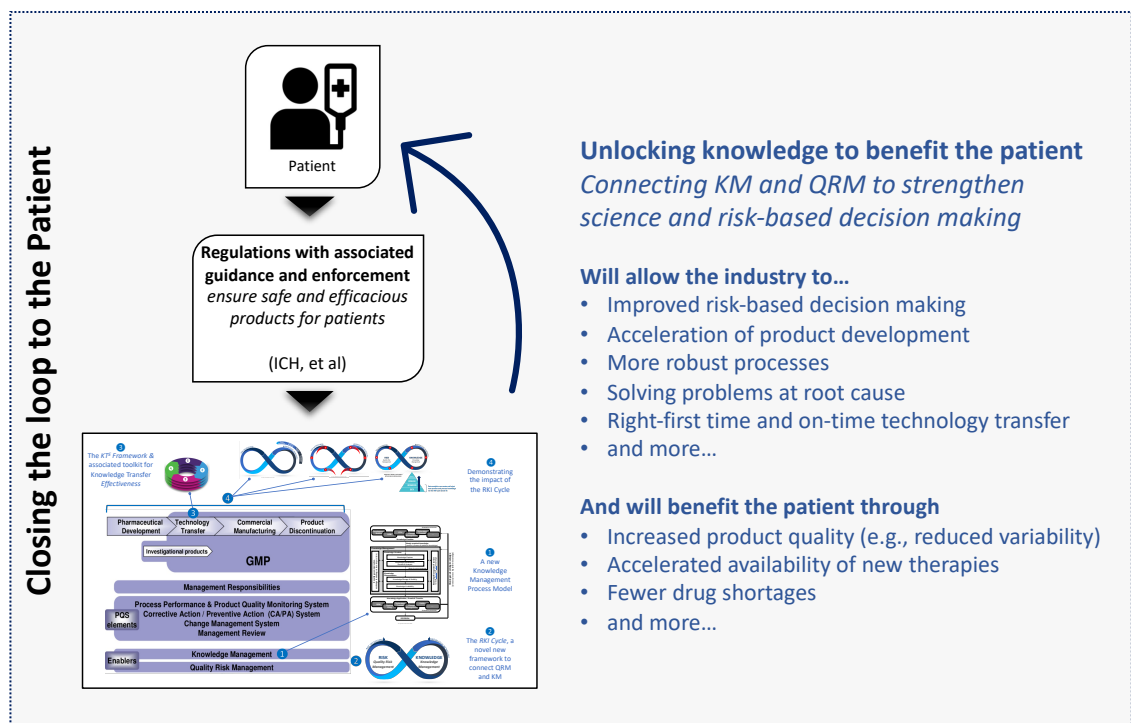


Figure 11-3 – Connecting this study back to the patient

Indeed, an opportunity to unlock knowledge is presented through the outputs and outcomes of this study with many promising and important benefits.

While this research study started with a focus on improving knowledge transfer for technology transfer (i.e., element 3 in Figure 11-2), this study has led the researcher on an exciting, educational, and thought-provoking journey which expanded the horizons of the researcher's knowledge, experience, perspectives, and influence. The opportunity to apply systems thinking and explore the intersections between the disciplines of QRM and KM in particular, as well as that of KM and data analytics, has been an enlightening opportunity. Doing such an exploration both across the pharmaceutical sector and on a global scale has made the experience all the more enriching for the researcher. This research study has allowed the researcher to reflect and engage with other stakeholders he would not normally have a reason to and to test new ideas. Furthermore, while the researcher has been a long time KM professional in industry, this research study allowed the researcher to shed the constraints of the views and association of a single company and explore perspectives and engage with audiences from across the sector.

An unavoidable reality that emerged during the course of this study was the global COVID-19 pandemic and the undeniable impact it had and will have on our society and the pharmaceutical sector. While COVID-19 impacts are still emerging, the impact of travel restrictions and market demand has already prompted changes to the industry (e.g., at least a temporary shift specifically in how technology transfers are done leveraging smart glasses and other technologies). In light of all of this, one must ponder:

- How effective is knowledge transfer in such scenarios?
- Employees are also being onboarded remotely, perhaps without even meeting their peer groups in person. How will relationships and trust develop?
- Will there be a surge of technology transfers to 're-shore' production within a country's home borders, to reduce supply chain risk and complexity, and reduce dependence of a nation's drug supply on other nations?

- How can the learnings about rapid product development and technology transfer be applied to accelerate access (and hopefully reduce cost) to future therapies, and what role can KM play?

It is anticipated that more of these scenarios will unfold over time. While this development did not change the course of the research study, it is quite possible that the COVID-19 pandemic may expedite the adoption of these outputs.

The researcher is gratified by the response to this study and all those who contributed, in ways big and small. The early results are promising, with the potential to drive a paradigm shift on how people think about knowledge management and its indispensable role in an effective PQS, and how knowledge management can be applied for meaningful and sustained benefits beyond the PQS.

The researcher hopes this study will have a significant and lasting impact on the pharmaceutical sector, through the outputs delivered and outcomes already in motion as a result of this study, and others to follow inspired by this study. This is especially relevant considering society is arguably facing a time of rapid and unprecedented change, already facing the complexity and need for speed with ATMPs, disrupted by the COVID-19 pandemic, and now confronting geopolitical forces which may well realign supply chains, and make accelerated development and new technologies the ‘new normal.’ Never before has it been more important to integrate knowledge and risk. Many exciting opportunities lie ahead, and the most important stakeholders of the industry’s success – the patients, who are not abstract and nameless entities but who are family members, friends, and colleagues – are waiting.

The next and final chapter in this research study, *Opportunities for Future Research*, will present a variety of topics to further examine to further extend the impacts of this research study.

Chapter 12: Opportunities for Future Research

The purpose of this chapter is to identify areas for future research. Although the researcher believes this study can help the sector take a step change forward in the adoption of KM and its connectivity with QRM, this study also explored many new aspects of KM and its interdependency with other disciplines. As such, many exciting research opportunities were identified, including the opportunity to directly advance the outputs from this study (e.g., through application guides or software applications) and to further explore many important interdependencies and adjacencies (e.g., data analytics). The following sections identify several exciting opportunities for further study.

12.1 Extension of the *Risk-Knowledge Infinity Cycle* Framework

One recommendation for future research efforts is to supplement the work done in this study with supporting materials to **extend and accelerate the impact of the *RKI Cycle* across the product lifecycle and to other elements within the PQS**. These concepts were briefly explored as part of this study, but further work is warranted to better position the *RKI Cycle* for expansion. As part of this effort, supporting materials such as an application or deployment guide with associated training to enable a team to quickly understand, apply, and benefit from the *RKI Cycle* will be needed. Additional case studies, both prospective (i.e., how the *RKI Cycle* can provide benefit) and retrospective (i.e., how the *RKI Cycle* could have provided benefit) can also assist in communicating and refining the framework. Other cases of how the framework can be applied should also be explored, such as to inform a learning curriculum. Furthermore, exploring commonality with other industries (e.g., aerospace, as identified during the confirmation exam feedback), is an opportunity to further extend the reach of the framework beyond the pharmaceutical industry.

12.2 Integrated knowledge management frameworks across the product lifecycle

A feature of this study was the focus on KM for the technology transfer stage of the product lifecycle. This study established a KM framework to standardise knowledge

management during technology transfer, the *Knowledge Transfer Enhancement (KTE) Framework*. The researcher believes **the underlying basis of a PDCA cycle as used for the KTE Framework as a closed-loop continual improvement process should be a suitable basis from which to build a KM framework for the other three stages of the product lifecycle** (product development, commercial manufacturing, and product discontinuation). Furthermore, a majority of the tools in the *KTE Toolkit* will also be portable across stages. Additional areas of focus could include:

- Further definition of practices specified in the *KTE Toolkit* (i.e., as identified in Table 7-1).
- A training package to support use of the *KTE Framework* and *KTE Toolkit*.
- A maturity model for knowledge transfer (including a gap assessment so companies can assess their current processes and quickly identify areas of improvement).
- Simplification of the *KTE Framework* and *KTE Toolkit* as warranted based on initial use and feedback.
- Exploration of the Information-space (“I-space”) model defined by Boisot (I-Space Institute, 2008) for mapping strategic knowledge. This model has been used to further define and prioritize mission-critical knowledge for complex industries, as described by Kennedy-Reid and Ihrig (Kennedy-Reid and Ihrig, 2013) and Ihrig and MacMillan (Macmillan and Ihrig, 2015), and could potentially be applied for each stage of the product lifecycle.

12.3 The link between knowledge management and data analytics

As introduced in Chapter 8, the link between KM and data analytics is an area of novel research that will better link data and data analytics more systematically into the PQS. The researcher sometimes describes this opportunity as the **‘vertical integration’ of the data-information-knowledge pyramid** (Figure 8-5). Given the industry focus on digital transformation (CIO, 2018), more data will become available, and the *RKI Cycle* and effective KM practices will be instrumental in how that data is surfaced as knowledge through data analytics, as illustrated in Figure 12-1.

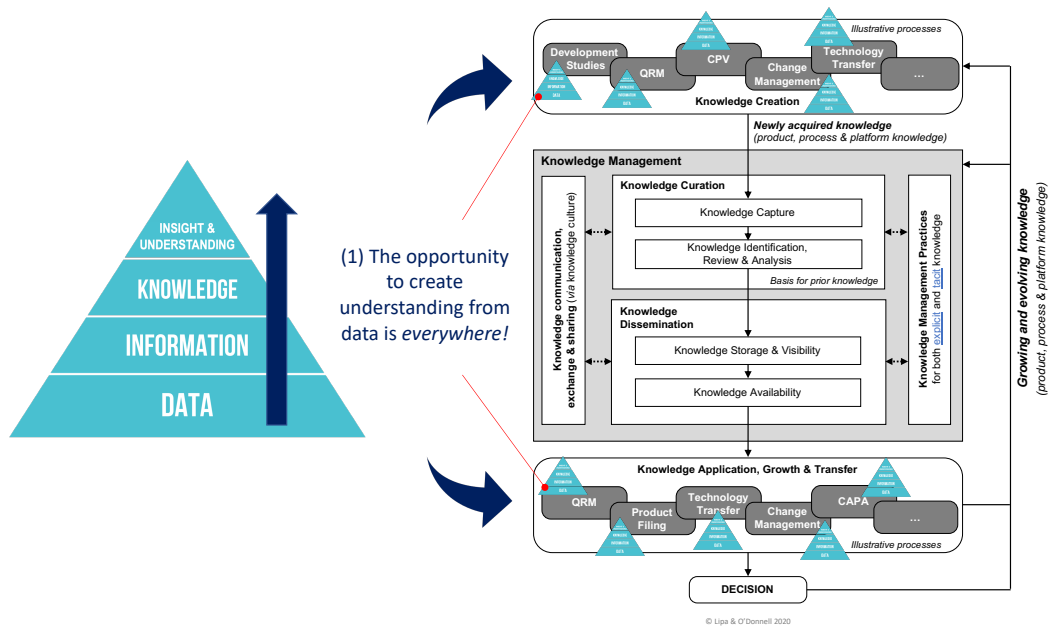


Figure 12-1 – The opportunity to feed KM from data and data analytics

12.4 KM competency building

It is likely KM could further benchmark the QRM journey towards effectiveness to seek other areas for development of guidance and supporting materials. One of these areas is that of KM competency building, through an associated KM competency model to define target competency levels, related training assets, and delivery thereof. This work could also define best practices for KM roles.

12.5 Additional opportunities

There are other, more focused topics of interest to the researcher that are not covered in detail as part of this research study which could benefit from further study, as follows:

- An expansion on **knowledge culture**, based on the work in this thesis.
- Further exploration and modelling of **knowledge leakage**, as characterised by the researcher in Chapter 6 (section 6.2.1).
- The concept of **‘democratisation of knowledge,’** and how to determine what knowledge is required on a role-specific basis, and how this knowledge can be ‘democratised’ to enable maximum efficiency and effective decision making.
- Topics introduced (or at least accelerated) by the **COVID-19** pandemic, including:
 - **Virtual technology transfers** and critical success factors, considering the principles for knowledge transfer during technology transfer presented

during this study in Chapter 6 and Chapter 7 (e.g., is remote support for a technology transfer using smart glasses as effective as a person in plant supporting the transfer?).

- How the outputs of this research study could be positioned to enhance the **potential wave of 're-shoring' technology transfers**, if such a need emerges, to increase speed, reduce cost, and help ensure sustained supply.
- Examining the feasibility and defining associated requirements for **applications** (e.g., checklists or gap assessments) **or other software to accelerate the reach and impact** of the *RKI Cycle* or *KT^E Framework* and *KT^E Toolkit* would be an area of valuable research, given the focus on digital. Such software applications would also support the standardisation, consistent use, and portability of the frameworks and supporting elements.
- Further explore the relevance and application of work by Teece et al. (Teece, Pisano and Shuen, 1997) on dynamic capabilities and strategic management, specifically that of dynamic knowledge based on increasing complexity (e.g., ATMPs) and accelerating rate of change for the industry (e.g., COVID-triggered acceleration of new therapies, merger and acquisition activity, etc.).

At the time of this thesis submission, work is underway to evaluate opportunities for further research on a variety of these topics. An immediate research project is being proposed in which the researcher will act as supervisor to a full time Ph.D. student, which will include (at a minimum) further exploration and development of the link between KM and the *RKI Cycle* to data analytics in partnership with PMTC. This proposal will also include an opportunity to follow up with NASA on the potential impact of the *RKI Cycle* for aerospace, as well as further exploration of how the *RKI Cycle* can support the sharing of lessons and risk-based decision making.

This research study has opened the door to many exciting opportunities, and the researcher is excited for the story to continue to unfold through these proposed next steps.

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Appendix 1 – Researcher’s Prior Experience

The researcher’s formative experience in knowledge management prior to commencement of this research study, presented in chronological order of events.

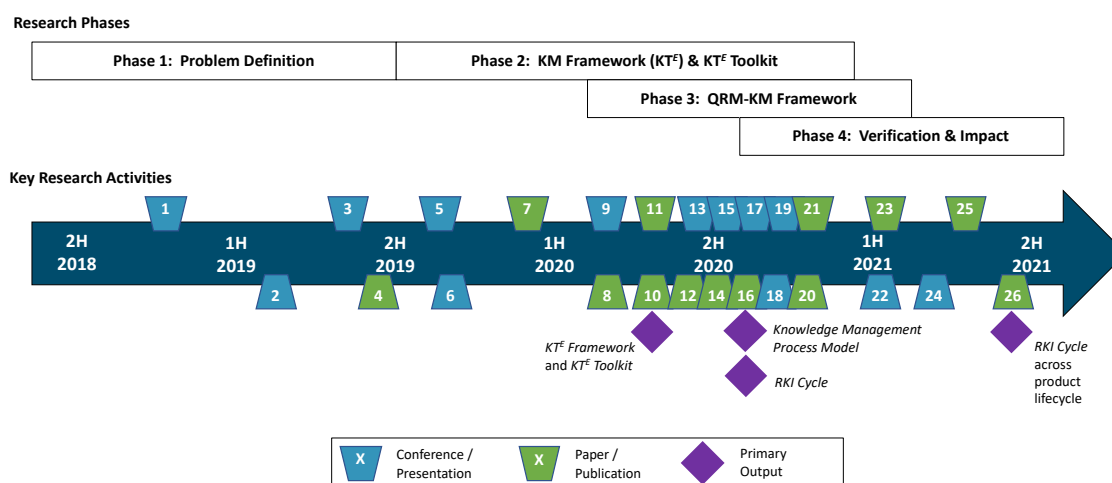
Experience / Activity / Event	Affiliation / Audience	Location	Description
FDA-Conformia-PhRMA Pharmaceutical Development / Risk Management Industry Workshop (12-13 Sep 2007) (FDA-Conformia CRADA, 2007)	FDA & Industry	Washington, DC	Member of MSD contingent
MSD Knowledge Management Strategy Kickoff Workshop (3Q 2007)	MSD internal	n/a	Facilitator
FDA-Conformia-PhRMA Summit - Pharmaceutical Development / Risk Management (20-21 Feb 2008) (FDA-Conformia CRADA, 2008)	FDA & Industry	Washington, DC	Member of MSD contingent
MSD KM Strategy Project initiated via Lean Six Sigma Black Belt Methodology (DMADV) (2008)	MSD internal	n/a	LSS Black Belt Certification
MSD Small Molecule Commercialisation KM Strategy 1.0 (2009)	MSD internal	n/a	Project Leader and Lead Author
Lean Six Sigma Black Belt Certification for development of KM Strategy (2009)	MSD internal	n/a	Black Belt Certification
Knowledge Management: Some Ways Industry is Addressing This. In <i>ISPE Washington 2010 Conference - FDA-ISPE Collaboration: Pharmaceutical Quality System</i> . (Lipa, 2011a)	ISPE	Washington, DC	Speaker & Panellist
Knowledge Management: An Iterative Process. In 2011 <i>ISPE/PDA/FDA/EMA Pharmaceutical Quality Systems (ICH Q10) Conference</i> (Lipa, 2011a)	ISPE, PDA, FDA, EMA	Arlington, VA	Speaker & Panellist
Knowledge Management: An Iterative Process. In 2011 <i>ISPE/PDA/FDA/EMA Pharmaceutical Quality Systems (ICH Q10) Conference</i> (Lipa, 2011b)	ISPE, PDA, FDA, EMA	Brussels, Belgium	Speaker & Panellist
KM Case Study: Combining Social Computing and Organizational Development Efforts into a Virtual Technical Network (VTN). In <i>APQC 2012 KM Conference</i> . (Guenard, Bruno and Lipa, 2012)	APQC	Houston, TX	Speaker & Panellist
Knowledge Management: An Iterative Process. In 2012 <i>PDA/FDA/JPMA/PMDA Pharmaceutical Quality Systems (ICH Q10) Conference</i> (Lipa, 2012)	PDA, FDA, JPMA, PMDA	Tokyo, Japan	Speaker & Panellist
Enabling a New Way of Working through Inclusion and Social Media: A Case Study. <i>OD Practitioner</i> , 45(4), 9-16. (Fall 2013) (Guenard <i>et al.</i> , 2013)	OD Practitioner	n/a	<i>Publication</i> - Author
Knowledge Management: An Iterative Process. In 2013 <i>ISPE/FDA Pharmaceutical Quality System (ICH Q10) Conference</i> . (Lipa, 2013)	ISPE / FDA	Beijing, China	Speaker & Panellist

Experience / Activity / Event	Affiliation / Audience	Location	Description
A Practical Approach to Managing Knowledge – A Case Study of the Evolution of KM at Merck. <i>Pharmaceutical Engineering</i> , 33(6). (2013) (Lipa et al., 2013)	Pharmaceutical Engineering	n/a	Author
Manufacturing Leadership Council 2014 Manufacturing Leadership Award (Workplace Leadership Category) for MMD's Virtual Technical Network (VTN). (Frost & Sullivan, 2014)	MSD internal	n/a	Award recipient
The Know-How and Know-Why: An Interview with Merck. <i>ISPE Pharmaceutical Engineering Supplement - Knowledge Management E-Journal</i> , 33(6), 20-24. (2014) (Calnan, 2014b)	Pharmaceutical Engineering	n/a	SME Interviewee
A Practical Approach to Managing Knowledge - Making Knowledge Flow in Merck's Manufacturing Division. In <i>APQC 2014 KM Conference</i> (Thien and Lipa, 2014)	APQC	Houston, TX	Speaker & Panellist
Knowledge You Need to Know. In <i>ISPEAK - The Official Blog of ISPE</i> . (2014) (Lipa, 2014a)	ISPE	n/a	Author
A Practical Approach to Managing Knowledge. In <i>2014 ISPE-FDA CGMP Conference</i> .	ISPE, FDA	Baltimore, MD	Speaker & Panellist
A Practical Approach to Managing Knowledge – A Case Study at Merck. In <i>2014 BioProcess International Conference</i> . (Lipa, 2014b)	BioProcess International	Boston, MA	Speaker & Panellist
A Practical Approach to Managing Knowledge: Making Knowledge Flow in Merck's Manufacturing Division. In <i>NASA Knowledge 2020 Conference</i> , NASA Kennedy Space Centre. (2014) (Lipa and Guenard, 2014)	NASA	Cape Canaveral, FL	Speaker & Panellist
2014 PDA Knowledge Management Workshop - Enabler for ICH Q8 - Q11, QRM and Continued Process Verification - Raising the Awareness (PDA, 2014a)	PDA	Bethesda, MD	Planning Committee & Breakout Moderator
A Practical Approach to Managing Knowledge in Merck's Manufacturing Division. In <i>KM Dublin 2015</i> . (Lipa, 2015)	Regulatory Science Ireland	Dublin, Ireland	Speaker
KM Dublin 2015 Symposium on Knowledge Management - From Discovery to Patient	Regulatory Science Ireland	Dublin, Ireland	Breakout Moderator
A Practical Approach to Managing Knowledge...2.0. In <i>NASA Knowledge 2020 Conference</i> , NASA Johnson Space Centre. (2015) (Lipa and Bruno, 2015)	NASA	Houston, TX	Speaker & Panellist
The Role of KM in Merck's Journey to World Class Supply. In <i>APQC 2015 KM Conference</i> . (Morrissey and Lipa, 2015)	APQC	Houston, TX	Speaker & Panellist
Kane, P., Lipa, M., & Hubert, C. (2015). Pharmaceutical Industry KM Focus Group Summary – APQC 2015. In <i>APQC KM Conference 2015</i> . (Kane, Lipa and Hubert, 2015)	APQC (pharma focus group)	Houston, TX	Facilitator
Steering Committee Member - <i>2017 APQC Knowledge Management Conference</i>	APQC	Houston, TX	Steering Committee Member
Helping the World Be Well: Knowledge Management in MMD. Guest lecture for <i>Information & Knowledge Strategy MS Program</i> , Columbia University, New York. (2016) (Lipa, 2016)	Columbia University	New York, NY	Guest Lecturer (Columbia University MS Program)

Experience / Activity / Event	Affiliation / Audience	Location	Description
Steering Committee Member - 2018 APQC Knowledge Management Conference	APQC	Houston, TX	Steering Committee Member
A Vision for Prior Knowledge – and How to Manage Knowledge as an Asset. In <i>CASSS CMC Regulatory Forum</i> . (2018) (Lipa, 2018a)	CASSS	Washington DC	Speaker & Panellist
Contributing book editor: <i>A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry</i> . (N. Calnan, P. Kane, M. Lipa, & J. Menezes, Eds.). CRC Press. (2018) (Calnan <i>et al.</i> , 2018)	Book Editor	n/a	Contributing Editor
Yegneswaran, P., Thien, M., & Lipa, M. Why Knowledge Management is Good Business, <i>A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry</i> (3-17), CRC Press. (2018) (Yegneswaran, Thien and Lipa, 2017)	Book Chapter Author	n/a	Author
Kane, P. & Lipa, M. The House of Knowledge Excellence - A Framework for Success. In <i>A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry</i> (181-224), CRC Press. (2018) (Kane and Lipa, 2018)	Book Chapter Author	n/a	Author
Lipa, M. & Schuttig, J. KM Evolution at Merck & Co., Inc.: Managing Knowledge in Merck Manufacturing Division. In <i>A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry</i> (243-260), CRC Press. (2018) (Lipa and Schuttig, 2018)	Book Chapter Author	n/a	Author
Steering Committee Member - 2019 APQC Knowledge Management Conference	APQC	Houston, TX	Steering Committee Member
Building Learning and Continuous Improvement into Everyday Work: The Quest to Learn Lessons in Merck Manufacturing. In <i>APQC 2018 KM Conference</i> . (Lipa and Schuttig, 2018)	APQC	Houston, TX	Speaker & Panellist
World Bank KM Forum - Working Smarter Together - Private Sector Panel	World Bank	Washington, DC	Panellist
Evolution of Merck Strategy for Managing Knowledge. Guest lecture for <i>Information & Knowledge Strategy MS Program</i> , Columbia University, New York. (2018) (Lipa, 2018b)	Columbia University	New York, NY	Guest Lecturer (Columbia University MS Program)

Appendix 2 – Details of Research Study Activities

This appendix provides details of all of the main study outputs including publications, conference presentations, panel discussions and other interactions to solicit feedback and disseminate this research to stakeholders across the sector. The figure below from Chapter 1 (Figure 1-5) provides a mapping of each activity onto the research timeline, and the table following provides the corresponding details for each activity numbered 1 to 26.



Activity	Research Activity / Output	Affiliation / Audience	Location	Description
1	Lipa, M. J. (2019) <i>Capture and Reuse of Critical Knowledge in an Evolving Workforce: A Model for Technology Transfer</i> . In 2019 PDA Annual Meeting.	PDA	San Diego, CA	Speaker & Panellist
2	Lipa, M. J. & Kane, P. E. (2019) Knowledge Management Research in the Biopharmaceutical Sector. In <i>An Audience with Regulators, Academia and Industry: The Role of Effective QRM & KM in Product Realisation for Patients in the 21st Century</i> .	PRST Conference	Dublin, Ireland	Speaker, Lead Author, Panellist
3	APQC Advanced Benchmarking (invitation only cohort of 5 companies across industries in KM)	APQC	Houston, TX	SME, Philosophical dialogue w/ other industries
4	Lipa, M. J., Kane, P. E. & Greene, A. (2019) <i>Effective Knowledge Transfer During Biopharmaceutical Technology Transfer: How Well Do We Do It?</i> Institute of Validation Technology (IVT), 25 (4).	IVT Network	n/a	Lead Author

Activity	Research Activity / Output	Affiliation / Audience	Location	Description
	Award recipient, Journal of Validation Technology 2020 Author of the Year			
5	Lipa, M. J., Kane, P. E., & Greene, A. (2019) <i>Effective Knowledge Transfer during Biopharmaceutical Technology Transfer – How well do we do it?</i> KENX Commissioning, Qualification & Validation University	KENX	Cork, Ireland	Conference Poster
6	Lipa, M. J. (2020) <i>Knowledge Management: Development of pragmatic industry guidance to benefit our patients & organizations.</i> In ISPE 2019 Annual Meeting & Expo.	ISPE	Las Vegas, NV	Speaker & Panellist
7	Guenard, R. et al. (2020) <i>A Test Case in CMC Business Processes from Late-Stage Development to Commercial Manufacturing.</i> BioPhorum Operations Group (paper and tool)	BioPhorum	n/a	Co-Author, Knowledge Map SME & facilitator
8	Kane, P. E. and Lipa, M. J. (2020) <i>Advancing Knowledge Management (KM) as an ICH Q10 Enabler in the Biopharmaceutical Industry,</i> Dublin: TU Dublin Academic Press	TU Dublin	n/a	Co-Author
9	Lipa, M. J. (2020) <i>Knowledge Management as a Pharmaceutical Quality System Enabler: How Enhanced Knowledge Transfer can help close the Q10 to Q12 Gap.</i> In 2020 PDA Europe	PDA	Virtual	Speaker & Panellist
10	Lipa, M. J., Greene, A., & Calnan, N. (2020) <i>Knowledge Management as a Pharmaceutical Quality System Enabler: How Enhanced Knowledge Transfer can help close the Q10 to Q12 Gap.</i> PDA Journal of Pharmaceutical Science and Technology July 2020 (accepted)	PDA Journal of Pharmaceutical Science and Technology	n/a	Lead Author
11	Kane, P. E., Lipa, M. J., Greene, A., & Calnan, N. (2020) <i>Knowledge Management Implementation: A Survey of the Biopharmaceutical Industry.</i> In ISPE Pharmaceutical Engineering - an Online Exclusive	ISPE Pharmaceutical Engineering	n/a	Co-Author
12	Lipa, M. J., Kane, P. E., & Greene, A. (2020) <i>Knowledge Excellence in the Lab: How Knowledge Management Can Enhance Lab Performance,</i> In <i>Quality Control Lab – A Crucial Contributor to Pharmaceutical Value Creation and Quality System Performance</i> (ed. T. Friedli et al)	Book Chapter Author	n/a	Lead Author
13	Lipa, M. J. (2020) <i>Reflections on a KM Journey.</i> Guest lecture for <i>Information & Knowledge Strategy MS Program,</i> Columbia University, New York.	Columbia University	New York, NY	Guest Lecturer (Columbia University)
14	Lipa, M. J., O'Donnell, K., & Greene, A. (2020) <i>Managing Knowledge and Risk – A Literature Review on the Interdependency of QRM and KM as ICH Q10 Enablers.</i> Institute of Validation technology (IVT), 26 (4).	IVT Network	n/a	Lead Author

Activity	Research Activity / Output	Affiliation / Audience	Location	Description
15	Podcast - Voices in Validation - Managing Knowledge as an Asset in the Biopharmaceutical Industry (recorded 11-Sep-2020)	IVT Network	Online	Speaker
16	Lipa, M. J., O'Donnell, K., & Greene, A. (2020) <i>Knowledge as the Currency of Managing Risk: A Novel Framework to Unite Quality Risk Management and Knowledge Management</i> . Institute of Validation technology (IVT), 26 (5).	IVT Network	n/a	Lead Author
17	Lipa, M. (2020) <i>Knowledge as the Currency of Managing Risk: A Novel Framework to Unite Quality Risk Management & Knowledge Management</i> . In PMTC Guide to Data Analytics for Pharmaceutical Manufacturing Launch.	PMTC	Virtual	Speaker & Panellist
18	"Establishing a "New Normal" for Pharma Quality Practices" in <i>2020 Bio/Pharma Virtual Congress</i> .	PharmaTech	Virtual	Panellist
19	Industry SME Reviewer (invited), PDA Technical Report No. 65, Technology Transfer	PDA	n/a	Invited as industry SME
20	Lipa, M, Kane, P., Greene, A. (2020) <i>Simple Practices to Facilitate the Flow of Valuable Tacit Knowledge during Biopharmaceutical Technology Transfer: A Case Study</i> , Level3, vol. 15, no. 2.	TU Dublin	n/a	Lead Author
21	Lipa, M, Kane, P., Greene, A. (2021) <i>Mapping KM Methods and Tools across the Pharmaceutical Product Lifecycle</i> , Level3, vol. 15, no. 2.	TU Dublin	n/a	Lead Author
22	Lipa, M. J. (2021) "Holding On to What You Know: Improving Knowledge Transfer to Reduce Risk and Benefit Patients," in <i>2021 PDA Annual Meeting</i> .	PDA	Virtual	Speaker & Panellist
23	Lipa, M., O'Donnell, K., & Greene, A. (2021) <i>A Survey Report on the Current State of Quality Risk Management (QRM) and Knowledge Management (KM) Integration</i> , Level3, vol. 15, no. 3	TU Dublin	n/a	Lead Author
24	Lipa, M. J., (2021) <i>Knowledge Management</i> , on invitation to the PDA Regulatory Affairs and Quality Advisory Board (15-Apr-2021)	PDA	Virtual	Invited industry SME
25	ISPE (2021b) <i>ISPE Good Practice Guide: Knowledge Management in the Pharmaceutical Industry</i> . Tampa, FL: ISPE.	ISPE	n/a	SME on Authoring Team
26	Lipa, M. J. et al. (2021) "Exploring the Risk-Knowledge Infinity Cycle (RKI Cycle) Across the Product Lifecycle," <i>ISPE Webinar</i> . (Note: This paper has been accepted by ISPE but not yet published. It will first be presented at a webinar scheduled on 20-May-2021.)	ISPE	n/a	Lead Author