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Solving the Continual Improvement and Innovation Challenge for the Benefit of Patients: How an Effective Pharmaceutical Quality System (PQS) and Risk-Based Approach Could Transform Post-Approval Change (PAC) Management

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SOLVING THE CONTINUAL IMPROVEMENT AND INNOVATION CHALLENGE FOR THE BENEFIT OF PATIENTS

How an Effective Pharmaceutical Quality System (PQS) and Risk-Based Approach Could Transform Post-Approval Change (PAC) Management

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Abstract

Patients deserve their medicines on time every time. Regulators safeguard public health by ensuring availability of safe, effective, high-quality medicines. Pharmaceutical companies must continually improve and innovate to deliver such medicines. In spite of these patient-centric objectives, drug shortages have continued to grow as a global public health concern. The drug shortage problem has existed for decades though there has been no shortage of effort, recommendations, papers, and expectations to resolve it. During the ongoing COVID-19 pandemic even exceptional measures were rapidly implemented to prevent shortages, yet no long-term solutions have been found.

This research hypothesis was that due to the high global regulatory complexity of making post-approval changes (PACs), pharmaceutical companies are slow in implementing new knowledge to continually improve and innovate their products and processes – even when this reduces risk to patients or improves the state-of-control. This results in sub-optimal operations, and eventually drug shortages.

To date, most efforts and solutions to tackle drug shortages by the industry or regulatory authorities have been from their individual respective perspectives. This research concluded that no one stakeholder can solve this 'wicked problem', and that its resolution lies in **practical standard solutions collaboratively developed and globally implemented across the pharmaceutical industry and its regulatory authorities**.

This research explored how an enhanced science and risk basis which considers current product and process knowledge within the framework of an effective Pharmaceutical Quality System (PQS) – could provide a clear pathway to overcome the global regulatory complexity, accelerate continual improvement and innovation, and help reduce drug shortages. It proposed that any PAC which can be demonstrated to not increase risk to product quality or patient safety should be implemented immediately within the construct of an effective PQS, without requiring prior regulatory approval; such changes would still remain under regulatory oversight through routine inspections that assess effectiveness of a company's PQS.

The research resulted in the development of standard practical solutions for the pharmaceutical sector - to enable regulatory flexibility, faster decision-making and implementation of PACs by allowing more changes to be managed in the PQS without requiring prior-approval. The research also defined what constitutes an effective PQS for PAC management, and how companies could demonstrate this during inspections, thereby shifting the regulatory oversight from review of individual PACs by assessors, to evaluation of the PQS effectiveness for PAC management by inspectors.

A portion of this research occurred during the COVID-19 pandemic. Given the pandemic is still ongoing, it did not assess implications or consequences of the "new normal" state that will emerge post-pandemic. However, the thesis touches on anticipatory considerations and poses relevant questions on how faster risk-based decision-making and collaborative models that emerged during the pandemic could and should continue as part of the "new normal".

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 (TU 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. TU Dublin has permission to keep, lend or copy this report in whole or in part, on condition that any such use of the material of the thesis be duly acknowledged.

20 Sept. 2021

Signature: _____ Date: _____

Emabelle Ramnarine

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Glossary of Terms and Abbreviations

1VQ for PAC	One-Voice-of Quality for Post-Approval Changes
AESGP	Association of the European Self-Medication Industry
APR	Annual Product Review
ATMP	Advanced Therapy Medicinal Product
CAP	Centrally Authorised Product
CAPA	Corrective Action Preventive Action
CDER	Center for Drug Evaluation and Research
CMD*h*	Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
CPV	Continuous Process Verification
CQA	Critical Quality Attributes
CQO	Chief Quality Officer
CRP	Collaborative Registration Procedure
CTD	Common Technical Document
DSPP	Drug Shortages Prevention Plan
EC	European Commission
EC	Established Condition
ECMP	Exceptional Change Management Process
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations

EFTA	European Free Trade Association
EGA	European Generic and Biosimilar Medicines Association (now called Medicines for Europe)
EIU	Economist Intelligence Unit
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
EUA	Emergency Use Authorization
EWG	Expert Working Group
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GPO	Global Purchasing Organisation
GMP	Good Manufacturing Practice. Also, cGMP, "current" Good Manufacturing Practice
HMA	Heads of Medicines Agencies
HPRA	Health Products Regulatory Authority (formerly Irish Medicines Board; Ireland)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (formerly International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICMRA	International Coalition of Medicines Regulatory Authorities
ID Testing	Identity Testing
IFPMA	International Federation of Pharmaceutical Manufacturers' Association

ISO	International Standards Organisation
ISPE	International Society for Pharmaceutical Engineers
KM	Knowledge Management
KOL	Key Opinion Leader
LIMS	Laboratory Information Management System
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
NCA	National Competent Authority
NMRA	National Medicines Regulatory Authority
NRA	National Regulatory Authority
OPQ	Office of Pharmaceutical Quality
PAC	Post-approval Change
PAC iAM℠	Post-approval Change Innovation for Availability of Medicines
PAT	Process Analytical Technology
PCMO®	Paradigm Change in Manufacturing Operations
PDA	Parenteral Drug Association
PIC	Pharmaceutical Inspection Convention
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PLCM	Product Lifecycle Management
PPPQMS	Process Performance and Product Quality Monitoring

PPTA	Plasma Protein Therapeutics Association
PQKMS	Pharmaceutical Quality Knowledge Management System
PQR	Product Quality Review
PQS	Pharmaceutical Quality System
PRST	Pharmaceutical Regulatory Science Team
QbD	Quality by Design
QMS	Quality Management System
QP	Qualified Person
QRM	Quality Risk Management
QSE	Quality, Safety, Efficacy
RAQAB	Regulatory Affairs and Quality Advisory Board
SCEC	Sub-Committee on Expert Circles
SRA	Stringent Regulatory Authority
TQM	Total Quality Management
TU Dublin	Technological University Dublin
UCD	University College Dublin
US	United States of America
WCBP	Well Characterized Biotechnology Pharmaceuticals
WHA	World Health Assembly
WHO	World Health Organisation

Table of Contents

List of Figures

List of Tables

Thesis Overview

This thesis submitted for the purpose of a PhD comprises of six parts across ten chapters that summarise the purpose, findings and key contributions from this research study. Important findings, unified pharmaceutical industry positions, and standard solutions resulting from this research study have been published by the researcher in various peer-reviewed journals. In order to improve readability of the work, these publications are discussed as appropriate and referenced throughout this thesis.

The following section provides the reader with an orientation of the six-part structure of this research thesis: The activities featured across the six parts were not in all cases conducted sequentially as the research study was iterative in nature.

Part One lays the foundation for this research study: Exploring the context of a problem resulting from global regulatory complexity that presents a barrier to continual improvement and innovation in the *pharmaceutical sector* (the term used throughout this thesis to refer collectively to pharmaceutical companies and regulatory authorities), which eventually contributes to the 'wicked problem' of drug shortages.

Part Two frames drug shortages as a global problem: Exploring what makes drug shortages global in nature and the detrimental consequences especially for patients. Given this context, why a response and the resulting solutions must also be global.

Part Three examines the pharmaceutical regulatory landscape: Exploring the vision and position of key pharmaceutical regulatory authorities (henceforth referred to as regulatory authorities throughout this thesis) on the global problem of drug shortages established in Part Two.

Part Four provides an overview on how the researcher brought the pharmaceutical industry together to create deeper awareness and understanding of current state challenges in assuring a reliable supply of safe, effective, high-quality medicines for patients, due to inadequate continual improvement and innovation.

Part Five focuses on the development of practical, standard, global solutions that facilitate effective delivery of medicines to patients. These solutions are a result of ongoing collaborative work within the pharmaceutical industry through the *1VQ for PAC Initiative* (established during this research), with ongoing input from regulators.

Part Six brings the research study to a close with a review of the outputs, outcomes, and impact of this research with recommendations for future research. It also articulates key learnings and opportunities brought forward by the pandemic.

Table 1 provides a summary of the six parts and corresponding chapters in this thesis.

Table 1: Thesis Overview

Part	Chapters
Part One: Research Study Foundations	• Chapter 1: Research Introduction and Context • Chapter 2: Literature Review • Chapter 3: Research Design, Methodology, and Methods
Part Two: Recognition of Drug Shortages as a Global Problem and the Need for Global Solutions	• Chapter 4: A 'Wicked Problem' – Drug Shortages in the Context of Inadequate Continual Improvement and Innovation • Chapter 5: Responding to the 'Wicked Problem'
Part Three: Exploring and Contributing to Regulatory Authorities' Positions in Context of the Research	• Chapter 6: Exploring and Contributing to Regulatory Authorities' Positions
Part Four: Unifying the Pharmaceutical Industry	• Chapter 7: The Importance of Bringing the Pharmaceutical Industry Together
Part Five: Practical Science and Risk-Based Solutions	• Chapter 8: Standard Solutions for the Pharmaceutical Sector
Part Six: Outcomes and Impact, Conclusions, and Opportunities for Future Research	• Chapter 9: Outputs, Outcomes, and Impacts of Research Study • Chapter 10: Research Conclusions and Opportunities for Future Research

Part One: Research Study Foundation

Part One lays the foundation for this research. It explores the context of a problem resulting from global regulatory complexity that presents a barrier to continual improvement and innovation in the pharmaceutical sector, which eventually contributes to the 'wicked problem' of drug shortages. This part is predominantly comprised of the foundational elements of pharmaceutical product quality, specifically:

- a Pharmaceutical Quality System (PQS)
- Quality Risk Management (QRM)
- Knowledge Management (KM)

It also considers the researcher's prior body of work which served as the starting point and continued throughout this research. It includes the following:

- Introduction, background and context for the research study (Chapter 1).
- A review of literature and guidance which provide the background for an effective PQS, QRM, KM, and their application to enable science and risk-based decision-making in relation to drug shortages and PAC management. It additionally highlights deficiencies in literature published thus far, some of which is being addressed by outputs from this research study (e.g., practical guidance and standard solutions for pharmaceutical companies on how to perform risk-based assessment of PACs), and some that still need to be addressed beyond this study (Chapter 2).
- An overview of the research design, methodology and methods used (Chapter 3).

Chapter One

Research Introduction and Context

Patients deserve to receive every dose of every medicine they need, every single day. They place their trust in regulators and pharmaceutical companies to provide them with a reliable supply of safe, effective, high-quality medicines. However, quality defects and drug shortages have been a constant struggle for patients, and these challenges have also impacted those in the sector including manufacturers and regulatory authorities.

In 2015, Dr Janet Woodcock, the then Center[1] for Drug Evaluation and Research (CDER) director at the United States (US) regulatory authority, Food and Drug Administration (FDA) and one of the most respected and outspoken international regulators, led the establishment of a new Office of Pharmaceutical Quality (OPQ), to present *One Quality Voice* in addressing the following pharmaceutical quality problems:

1. High occurrence of product recalls and product defects
2. Alarming shortages of critical medicines, many due to outdated equipment, aging facilities, and lack of effective quality management systems
3. A burdensome regulatory framework that requires manufacturers to submit post-approval supplements as they strive for process optimisation (partly because of the current practice of "locking in" an applicant's manufacturing process before it is fully optimised)
4. Current regulatory review and inspection practices that tend to treat all products equally, without considering specific risk to consumer or individual product failure modes
5. The fact that FDA only gets limited information about current state of pharmaceutical quality with no formal means for quality surveillance except through inspections, where inspection findings are not a reliable predictor of the state of quality

[1] The US spelling of the word 'Centre' is being used throughout this thesis when referring to the US FDA Center for Drug Evaluation and Research to be consistent with its US origin

6. The fact that inspections are not well-connected to knowledge gained from product reviews, and product reviews are based on pre-marketing data instead of the conditions under which the product is manufactured during commercial production (FDA, 2015)

In 2019, in an FDA Voices article titled *'To Help Reduce Drug Shortages, We Need Manufactures to Sell Quality – Not Just Medicine'* (Woodcock, 2019), Dr Woodcock identified a critical element to quality in pharmaceutical manufacturing as:

> *'the ability to reliably make the product in sufficient quantities and with sufficient speed to ensure that supply consistently meets demand over sustained periods of time. This is especially true in the pharmaceutical industry, where the product is often life-sustaining — and ongoing access is critical.*'

In 2012, the researcher also set about exploring this topic of drug shortages through her activities as a member of the Parenteral Drug Association (PDA). PDA, a leading global provider of science, technology and regulatory information, is a non-profit international professional association of more than 10,000 individual member scientists with an interest in the fields of pharmaceutical, biological, and device manufacturing and quality (PDA, 2021). PDA creates awareness and understanding of important issues facing the pharmaceutical and biopharmaceutical community; it therefore, provided the researcher a useful industry platform to discuss this topic.

Specifically focusing on risk-based applications to prevent and manage drug shortages, the researcher led a PDA Drug Shortage Task Force between 2012-2015, the output of which was published as PDA Technical Report 68, *Risk-Based Approach for Prevention and Management of Drug Shortages* (Ramnarine *et al.*, 2014). A key insight the researcher gained during the development of Technical Report 68 was that a contributing factor to manufacturing issues, quality defects, and drug shortages was the slow pace of adoption of new technologies and a reluctance to continuously improve within the pharmaceutical manufacturing sector. The researcher suggested that solving the ***continual improvement and innovation challenge*** could help address the drug shortage problem and benefit patients. In this context, it is useful at this point to consider how medicines are approved prior to marketing to patients.

Medicines are developed by pharmaceutical companies and applications are submitted to regulatory authorities (as regulatory filings) for approval, prior to putting any

medicine into commerce and making it available for patients in a country or region. Once a medicine has been approved by a regulatory authority and launched (i.e., made available to patients) within a country or region, any change that is made to the product post-approval, or which affects its manufacturing facilities, manufacturing processes, raw materials, analytical methods, or any third-party suppliers, is called a post-approval change (PAC). Continuous improvement by definition, requires that changes be made, and today, when a PAC is needed, most must be submitted as a regulatory filing for approval by assessors at each of the regulatory authorities that approved the initial product application.

This process, while appearing to be relatively straightforward from a regulator's perspective, typically proves to be a great challenge from a pharmaceutical company's perspective, who may have their products on sale in several countries and regulatory jurisdictions. This means that companies need a PAC to be approved by all those countries before it can be implemented, and this can often take several years. In order to focus on this conundrum, and advance the insights gained during the development of PDA Technical Report 68, the researcher in 2016, formed a PAC-specific Task Force within PDA, called Post-Approval Change: Innovation for Availability of Medicines (PAC iAM^{SM}) Task Force. The outputs of this Task Force are discussed in Chapter Seven, section 7.1.

Figure 1.1, developed by the researcher and Dr Anders Vinther in 2019, for the first time articulated in visual format the view of a single PAC from a regulatory authority's perspective versus that from a pharmaceutical company's perspective, where the PAC requires approval sometimes in 100+ countries.

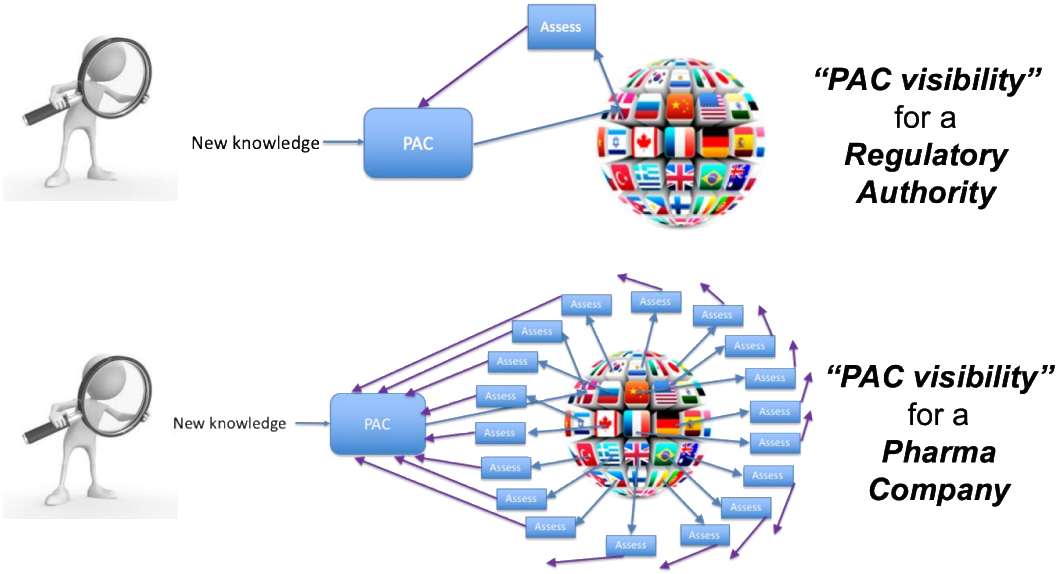

Figure 1.1: Post-Approval Change View for a Regulatory Authority vs. a Pharmaceutical Company

In reality, a pharmaceutical company may be managing several hundred PACs at any given time; consequently, their perspective of this is better depicted in figure 1.2 below:

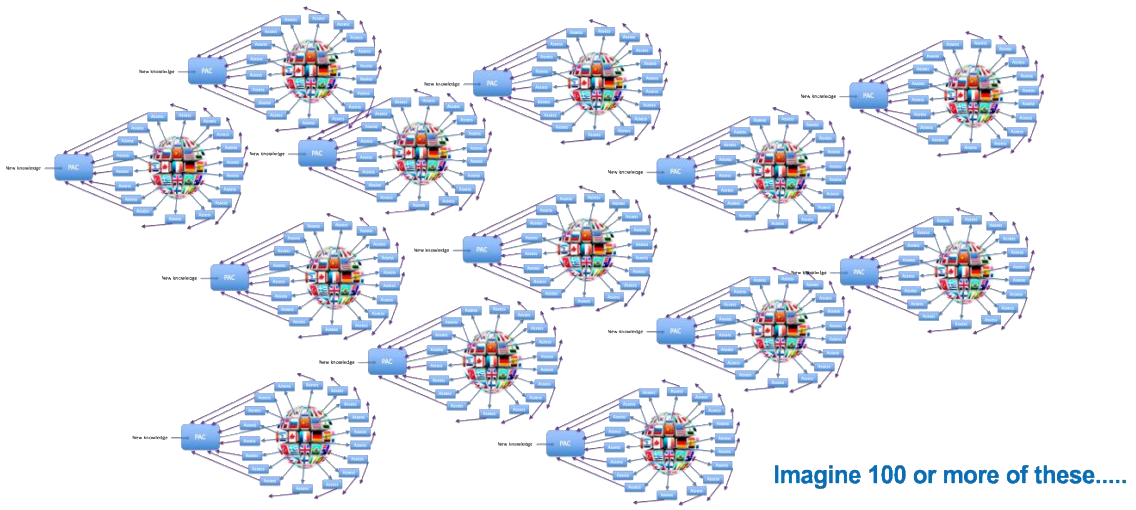

Figure 1.2: Reality of Many Concurrent PACs for a Pharmaceutical Company

These two graphical illustrations have become widely used and referenced by both pharmaceutical companies and regulators, as they served to raise awareness, educate each stakeholder segment on the implications of the problem, and bring a common understanding of the problem to the pharmaceutical industry and regulatory authorities alike.

In 2019, the researcher and Vinther met with Dr Woodcock to discuss PACs and the significant challenge with continual improvement and innovation in a global environment. At this meeting the researcher shared the images above, outlined the current complexities with global PAC management and raised the question of how the pharmaceutical industry could build trust with regulators so that more changes could be managed within a company's PQS and without requiring prior-approval from the regulator?

Upon seeing the two graphics on the current state (Figures 1.1 and 1.2), Dr Woodcock acknowledged a serious problem existed and that neither regulatory authorities nor pharmaceutical companies were working together as they could and should, to collectively and globally address this issue. She noted that the current ways of addressing this topic through different pharmaceutical industry associations and volunteer-based activities, albeit well-intentioned, were not making sufficient progress in addressing the problem. To resolve this, she specifically asked the researcher and Vinther to unite Senior Quality Leaders in the industry (as they are the accountable owners of product quality-related decisions and the PQS within their companies), with a view to developing standard pharmaceutical industry solutions for PAC management.

At the time (2017-2018), the researcher was enrolled at the Stanford Graduate School of Business in a Corporate LEAD Innovation Certificate Program, which focused on design thinking and the innovation process, building business models and organization design for innovation, overcoming resistance to change, critical thinking, and negotiation strategies. The program equipped the researcher on methodologies and tools to engage, accelerate and disrupt for meaningful, impactful change.

Taking the learning from the LEAD program, building on Dr Woodcock's vision of *One Quality Voice* for regulators, and with the aim to unify senior leaders in the pharmaceutical industry, in 2018 the researcher transitioned the volunteer-based PDA PAC iAM^{SM} Task Force into a *One-Voice-of-Quality for PAC (1VQ for PAC) Initiative* for the industry, sponsored by the Chief Quality Officers (CQOs) of the top 25 global pharmaceutical companies. This was the first time that Senior Quality Leaders in the industry united to speak with one voice in addressing this challenge. And to unite regulators globally on this topic as well, Dr Woodcock set in motion mechanisms

whereby assessors and inspectors could come together in their respective circles to find solutions; details of these are discussed in Chapter Six.

Dr Woodcock and the researcher are not alone in their desire to ensure the reliable supply of safe, effective, high-quality medicines to patients. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), an international non-profit association that brings together regulatory authorities and the pharmaceutical industry, aims to:

> "*achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner*." (ICH, 2021)

For well over 15 years, ICH has consistently developed and established guidances such as ICH Q9 *Quality Risk Management* (ICH, 2005c), ICH Q10, *Pharmaceutical Quality System* (ICH, 2008), and the latest one, ICH Q12 *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (ICH, 2019), yet the objective of reliable supply of safe, effective, high-quality medicines for patients, has yet to be accomplished. Numerous new and revised regulations, papers and positions advocating for QRM, KM and continual improvement have been developed, yet the issue of drug shortages persists.

This research seeks to explore why this is the case, why in spite of the existence of ICH Q9, Q10 and more recently Q12, drug shortages still persist, and how 'slow' continual improvement and innovation in the pharmaceutical sector might be contributing to the growing problem of drug shortages. Specifically, the research focuses on how an effective PQS and a science and risk-based approach could transform PAC management, enabling timely implementation of changes (i.e., continual improvement) which would enhance and improve pharmaceutical manufacturing.

The researcher proposes that a company which demonstrates it has an effective PQS and which applies science and risk-based assessments to PACs, should be able to implement certain PACs without regulatory prior-approval where it determines no or minimal impact of the change to product quality or patient safety. Such changes could still be reviewed by inspectors during their inspections of companies to ensure that the company's PQS was indeed effective in handling these PACs. In other words, while the

regulatory oversight would shift from the ***assessors'*** [2] review and approval of each PAC to the ***inspectors'*** [3] evaluation of the overall effectiveness of a company's PQS in managing these PACs, there would still be regulatory oversight; it however, would be in a manner that would facilitate faster continual improvement and innovation.

The study first explored the global complexity associated with continual improvement and innovation within the pharmaceutical industry, and the barriers that existed. It examined why this was such a significant challenge, and, as the study progressed, it became evident that addressing the problem required collaborative work across a broad and diverse stakeholder community, including pharmaceutical companies, regulatory authorities, policy makers, healthcare providers, patient care and advocacy groups, governments, and society as a whole.

The research plan was designed to examine the problem primarily through the lens of the frontline stakeholders, ***pharmaceutical companies*** and their ***regulators***. It excluded the exploration of policies or policy makers, legislation or legislators, healthcare providers, patient care and advocacy groups, governments and society at large. Nevertheless, the study reaffirmed the interconnectedness within these aspects and their implications for public health, pharmaceutical regulations, and a marketing authorisation holder's (MAH) ability to reliably supply medicines to patients.

This chapter outlines the overall context, intent, scope and objectives of this research study. It introduces the researcher and lays out the researcher's pre-study work that led to undertaking this research.

1.1 Background

Pre-research study work on this topic was initiated in 2012 as part of the researcher's pharmaceutical industry affiliation; this was 6+ years before this research was registered for a PhD with the Technological University (TU) Dublin, and although that prior work by the researcher had not been organised under a formal study, some of it was extended and deepened via this research study with TU Dublin. It provided an important

[2] Assessors are those who review and approve product regulatory submissions at a regulatory authority.

[3] Inspectors are those who inspect pharmaceutical companies, including their PQS.

foundation for the research undertaken in this PhD. Key elements of the prior work were specifically relevant to certain aspects of this study and are discussed within the appropriate chapters of this thesis. An overall summary is also provided in Appendix I.

Figure 1.3, developed by the researcher, illustrates the interconnectedness between:

1. The ultimate objective of ensuring an uninterrupted reliable supply of safe, effective, high-quality medicines to patients and the stakeholder community involved in accomplishing this objective (shown in the top stratum of the figure)
2. The foundational regulatory framework and expectations laid out by ICH in its guidances:
    a. ICH Q12 on product lifecycle management (shown in the middle stratum), and
    b. ICH Q9 and Q10 that provide the foundational bases for Q12 in relation to QRM, KM and PQS (shown in the bottom stratum of the figure)

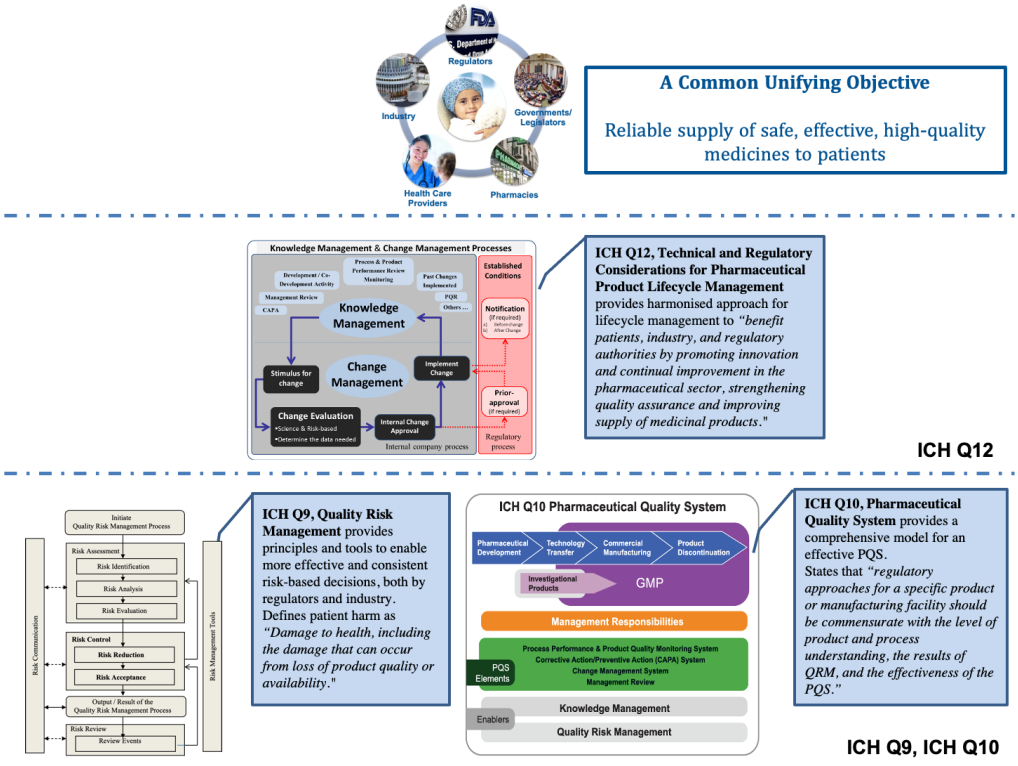

Figure 1.3: Connecting Risk, Knowledge and Lifecycle Management (within an Effective PQS) to Deliver Value for Patients

The researcher's aims for this study were to:

- Explore the challenge and root cause of slow continual improvement and innovation in the pharmaceutical sector
- Assess how a science and risk basis and timely KM, within the construct of an effective PQS, might be a suitable lever in addressing the challenge
- Use the findings to design practical standard solutions for the pharmaceutical industry that, when implemented, would accelerate continual improvement and innovation, making a meaningful contribution towards reducing drug shortages and improving the timely availability of medicines for patients globally

1.2 Research Context – Framing the Problem to be Addressed

The problem this research seeks to address has several facets, but at the heart of it is the premise this chapter opens with, that:

> *'Patients deserve to receive every dose of every medicine they need, every single day.'*

As described in the introduction, there is a gap between what patients deserve and what they get. This research specifically seeks to explore ways to address this gap. To set the context, the problem will be discussed under the following headings:

- The burden of high global complexity with respect to PACs
- The potential link of this burden to drug shortages
- The PQS as a potential means to reduce this burden

1.2.1 The Burden of High Global Complexity

The globalisation of pharmaceutical manufacturing and supply has continued to evolve over the last few decades. It is an unavoidable reality primarily resulting from geopolitical, economic, business and supply chain factors to list a few. From a patient's perspective the complexity it introduces is not ideal. This research acknowledges the high global complexity but does not attempt to reduce it; rather it addresses what the pharmaceutical sector (as a key stakeholder) could do to reduce the burden it leads to.

Post-Approval Changes

Pharmaceutical companies have become increasingly global in the manufacturing and marketing of their products. Before a product can be marketed in any country, it must be

approved by the regulatory authority in that country or region to ensure that it meets their regulatory and legal expectations. A globally marketed product can often be distributed in as many as 100+ countries, and, as such, it needs to be approved by the regulatory authority of each of those 100+ countries, or within their regions. Once a product has been approved by the regulatory authority and launched within a country or region, most changes made post-approval to the product, its manufacturing facilities, manufacturing processes, raw materials, analytical methods, or any third-party suppliers - known as post-approval changes, or PACs, must also be approved by the same regulatory authorities that approved the initial product application.

During the commercial life of a product, PACs are inevitable as new knowledge and experience with the product is gained. PACs are needed to maintain a state of control and drive continual improvement. Reasons for PACs include (but are not limited to):

- upgrades to aging equipment and facilities
- supplier changes
- implementation of new regulatory requirements
- improvements needed to raw materials
- changes to manufacturing processes (e.g., to improve consistency, reduce variability, improve yields etc.)
- addition of new sites or equipment to increase manufacturing capacity
- addressing quality issues, manufacturing issues and/or compliance gaps
- responding to signals and trends (e.g., from product quality reviews, corrective and preventative actions (CAPAs), operational reviews, management reviews)

As this research progressed, a number of standard solutions for PAC management (based on the premise of reduced regulatory complexity and an increased use of the PQS, supported by QRM and KM) were developed. A total of 13 PAC examples were selected and evaluated within the context of those standard solutions, and that work directly led to a number of industry *1VQ for PAC* position papers. Those examples and position papers are discussed in Chapter Eight, section 8.6 of this thesis.

Today many PACs require a regulatory filing and an individual approval by each country where the product is marketed before the changes can be implemented. To illustrate the scale involved, a global vaccine company is known to submit up to 8000

PACs in a year that need either approval by (or at least a notification to) the regulatory authority in each country their products are marketed in, prior to PAC implementation. In discussions with multiple companies, it was noted that greater than 99% of such PACs submitted to regulatory authorities were approved. This raised a logical question:

> *if >99% of submitted PACs were approved by the regulatory authorities, could a company not make decisions on some of these PACs without having to submit and wait for regulatory authorities from each of the 100+ countries to approve them?*

The issue is not as much that 100+ countries must approve a PAC, but that obtaining approval from all these countries takes a very long time, and this introduces complexity and risk. Global approval for a single PAC can often takes years (sometimes 5+ years) because of the varying timelines and requirements (that add significant workload for PAC submissions) across the regulatory authorities in each of these countries. Until the time a PAC has been approved and implemented in **all** relevant countries, a company must maintain and produce product in both the pre-change and post-change state for each country, in order to be compliant with each country's regulatory expectations. This means that a company has to maintain inventory of product manufactured both by the pre-change and post-change state, and ensure that the post-change state product is only sent to those countries that have already approved the change; countries that have not yet approved the change must receive product manufactured by the pre-change state. For a company, replicating this pre-change and post-change state across 8000 PACs a year across its product portfolio very quickly results in a product inventory comprised of hundreds of versions of the same product, pre-change and post-change state. This leads to highly complex and challenging product inventory and supply logistics which present numerous opportunities in daily manufacturing and supply operations for potentially serious errors due to multiple versions of a process or product being in place at the same time. The risk is that an unapproved version of the product gets supplied to a country that has not yet approved and given the clearance for the related PAC, or that a country has approved a PAC related version yet receives the pre-change version of the product.

But arguably, the more important issue is that such massive global complexity has severely hindered and disincentivised continual improvement, innovation, and the timely implementation of knowledge gained during commercial operations in

pharmaceutical companies - even when doing so can result in a reduction of risk to product quality or patient safety, accelerate product and process improvements, or close compliance gaps. On the contrary, this current global PAC complexity has created the opposite undesired effect: a disincentive to pursue continual improvement, innovation and meaningful change in favour of the current state and status quo. Pharmaceutical companies that maintain status quo may even have a financial advantage over companies that continually improve and innovate, because the cumulative global cost of filing a PAC and maintaining a complex inventory of multiple product versions during the long transition state until a PAC is approved globally, is a heavy burden for many companies. It can rapidly outweigh the long-term benefits of continual improvement and innovation. This can eventually result in drug shortages and impact public health, because of a company's failure to upgrade its aging facilities, equipment, processes, materials and methods. It can also eventually impact the viability of a product and perhaps the company. This has been evident in several instances of aging facilities and equipment, where companies had not upgraded their older equipment and facilities, and were ultimately unable to meet cGMP and regulatory expectations, let alone continually improve. Innovation typically precedes regulation change. As Peter Drucker stated:

> "*The enterprise that does not innovate, inevitably ages and declines. And in a period of rapid change such as the present entrepreneurial period, the decline will be fast."*(Drucker, 1993)

The Common Technical Document (CTD)

For regulatory review and approval, all Quality, Safety and Efficacy information for a product is assembled in a common format called a Common Technical Document (CTD). The CTD is organised into five modules - Module 1 is region-specific, while Modules 2, 3, 4 and 5 are intended to be common for all regions (ICH M4, 2000). At its first approval, a product is typically approved for one indication and it has one registered manufacturing process, as submitted to regulatory authorities in the CTD format. During its commercial life, the product may remain the same, the indication may remain unchanged – yet, due to the many PACs necessary during the commercial life of the product, the company has to maintain different inventories associated with each PAC until the PAC has been approved across all countries. This significantly lowers a company's ability to respond to a change in demand signals for a specific

product version, eventually resulting in shortages even when acceptable product versions are available and a shortage could in theory be entirely avoided.

Example from a Global Vaccine Manufacturer's Perspective

Currently, from a regulatory perspective, individual PACs are essentially treated the same across all companies, in that, the level of product and process knowledge, and the effectiveness of the company's PQS in managing PACs, are generally not taken into account by regulators when regulating those PACs. In addition, the same PAC may sometimes receive varying approval decisions from different regulatory authorities, even though the science and risk-based assessment for the PAC remains exactly the same for each country that it is submitted to. Figure 1.4 is a real example from a global vaccine company that illustrates the global PAC complexity for a single PAC. This is not an uncommon scenario – it is experienced by most global companies with products marketed in multiple countries. The example shows that different decisions are being made for the same PAC even though the risk to product quality or patient safety remains unchanged. Additionally, there is limited transparency (for a company from a regulatory authority, and between regulatory authorities) on the process and considerations regulatory authorities use in making these PAC decisions.

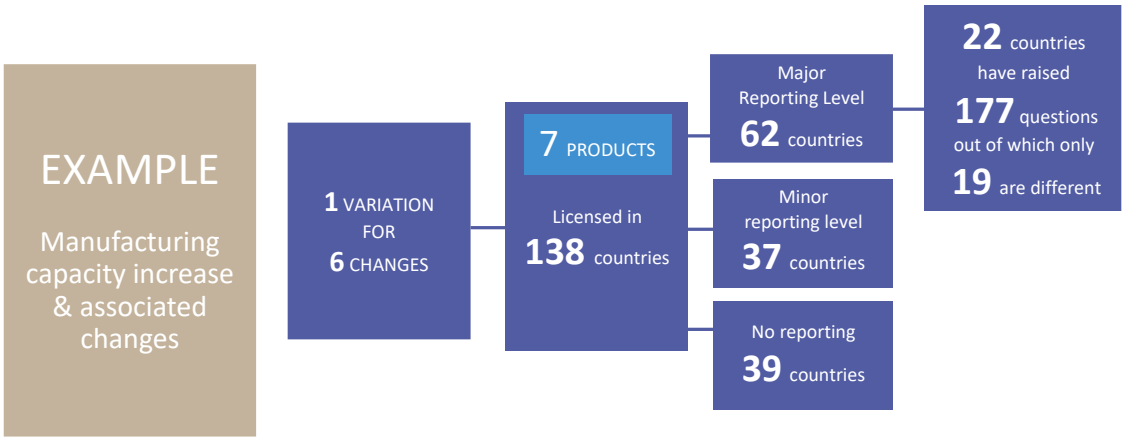

Figure 1.4: Global PAC Complexity for One Change – An Example from One Pharmaceutical Company

As discussed in the introduction to this chapter, in January 2019 the researcher and Vinther met with Dr Woodcock, Head of CDER at the US FDA (hereafter referred to as FDA) and senior leaders from her staff, including Dr Ashley Boam, Rapporteur for the ICH Q12 guidance that was in development at the time. The meeting was to discuss

PACs and the significant challenge with continual improvement and innovation in a global environment. At this meeting the researcher and Vinther laid out the current complexities with global PAC management and raised the question of how the pharmaceutical industry could build trust with regulators so that more changes could be managed within a company's PQS.

Dr Woodcock acknowledged the gravity of the problem and that neither regulatory authorities nor pharmaceutical companies were working together as they could and should to collectively reduce this global complexity. This discussion catalysed two significant actions:

1. Establishment of a pharmaceutical industry *1VQ for PAC Initiative* in 2019
2. Launch of a strategic initiative in 2021 by the International Coalition of Medicines Regulatory Authorities (ICMRA), a strategic coordinating, advocacy and leadership entity of regulatory authorities, on a global Product Quality Knowledge Management System (PQKMS) that would enable:

   "more extensive mutual reliance among regulators through work to ***harmonize specific data expectations for sponsors*** *and* ***standards for review among regulators****, so that regulators can be assured of the comparability of the assessments and related determinations of other regulatory authorities on whom they intend to rely."*(ICMRA, 2021)

Further details and outcomes from this January 2019 meeting, the *1VQ for PAC Initiative*, and the ICMRA strategic PQKMS initiative are described in Chapter Six and Chapter Seven of this thesis.

1.2.2 The Potential Link of the Global Complexity Burden to Drug Shortages

Drug shortages are a global problem; they are not localised to certain countries or regions, and therefore, local solutions cannot sustainably resolve this problem. In spite of appreciable advancements in regulations and technologies since the beginning of the 21st century, which are discussed in detail in Chapter Two of this thesis, the problem of drug shortages has continued to worsen. The researcher contends that:

> *the enormous complexity associated with global PAC management delays resolution of cGMP compliance or quality issues and continual improvement to such an extent, that it potentially contributes to exacerbating the issue of drug shortages.*

This linkage between undesirably slow continual improvement and innovation and drug shortages was first suggested and described as what is termed a 'wicked problem' by Vinther in an article in the PDA Letter (Vinther, 2016). The concept of a 'wicked problem' is defined and explained in Chapter Four of this thesis. The current situation is contrary to what every stakeholder wants, in spite of the best intentions and commitment to provide a reliable supply of safe, effective, high-quality medicines to patients.

A regulatory framework that supports the availability of safe, effective, high-quality medicines for patients is a vital component within the pharmaceutical environment. However, the increased globalisation of the pharmaceutical industry at the same time as increased regionalisation of regulatory frameworks, along with the complexity added by increasing and varying submission documentation requirements, have contributed to a state of dysfunction, and is hindering this very objective. Though more World Health Organisation (WHO) countries have strengthened their regulatory systems in accordance with the World Health Assembly's (WHA) direction given in WHA67.20, *Regulatory System Strengthening for Medical Products* (World Health Assesmbly, 2014), this has had the unintended consequence of every country adding often country-specific requirements. This has had the impact of further increasing the PAC processing times in these countries, and aggravating the regulatory complexity problem.

All of this global complexity causes a significant time lag between the acquisition of new knowledge about products and their manufacturing processes, and the implementation of such new knowledge into daily operations. Regulatory oversight, designed to safeguard public health, has, on account of this global complexity, paradoxically and unintentionally contributed to a loss in the state of control and to challenges with product availability. The increased global burden of PAC management and the resulting complexity in product lifecycle management are potentially compounding the drug shortage problem.

Several regulatory authorities have identified that most drug shortages are caused by manufacturing and/or quality issues (European Commission, 2012). The researcher explored this specific aspect in her discussions with pharmaceutical companies, both in her pre-research work and through the *1VQ for PAC Initiative* focus groups (described

in Chapter Seven of this thesis). In applying the *Five Whys* technique, a simple and effective approach to systematic problem-solving (Serrat, 2017), in her inquiry, the following responses were noted:

- Why do you have a drug shortage?
    - because of manufacturing and/or quality issues
- Why do you have manufacturing and/or quality issue?
    - because facilities or equipment are aging, or processes and methods haven't been brought up-to-date
- Why have aging equipment, processes or methods not been updated?
    - because the global regulatory complexity is too high and a PAC takes a long time or significant effort, making it easier to maintain status quo

This link between global regulatory complexity being an aggravating factor for the lack of continual improvement and that in turn contributing to drug shortages is noted in a research conducted by the Economist Intelligence Unit (EIU) (EIU, 2018), and is explored in further detail in Chapter Four and Chapter Five of this thesis.

1.2.3 The Pharmaceutical Quality System (PQS) as a Means to Reduce the Burden of Global Complexity

The Pharmaceutical Quality System (PQS)

In 2005, ICH recognised the need for a guideline describing a:

> "*modern quality system to establish and maintain a state of control that can ensure the realisation of a quality drug product and facilitate continual improvement over the lifecycle of a drug product."* (ICH, 2005b)

The PQS model as envisaged by ICH was intended to augment current Good Manufacturing Practices (cGMPs) and reflect the concepts of a Quality Management System (QMS) defined by the International Organisation for Standardisation (ISO), an independent, non-governmental international organisation. Even back in 2005, the perceived problem with regional differences in regulatory requirements was that they could lead to varying interpretations and potential divergence, resulting in:

- *"fragmented or fundamentally divergent approaches to quality systems*
- *delays in the availability of medicines to patients around the world*
- *delays in the implementation of innovation and continual improvement for existing products due to different expectations*

- *delays in the launch of new products,* and
- *different approaches to compliance inspections."* (ICH, 2005b)

The ICH Q10 Concept Paper envisioned the encouragement of science and risk-based approaches to quality decisions, facilitation of innovation and continual improvement throughout the entire product lifecycle, and demonstration of pharmaceutical industry and regulatory commitment to robust quality systems and technical innovation, along with assurance of consistent availability of medicines.

Consistent with that Concept Paper, ICH Q10, *Pharmaceutical Quality System*, was approved in 2008 (ICH, 2008). It established a comprehensive PQS model across the product lifecycle (pharmaceutical development, technology transfer, commercial manufacturing and product discontinuation) with three specific objectives:

1. *Achieve product realisation*
2. *Establish and maintain a state of control, and*
3. *Facilitate continual improvement*

The PQS model identified four PQS elements (Process Performance and Product Quality Monitoring System (PPPQMS), CAPA System, Change Management System and Management Review), along with two enablers (KM and QRM), as depicted in Figure 1.5.

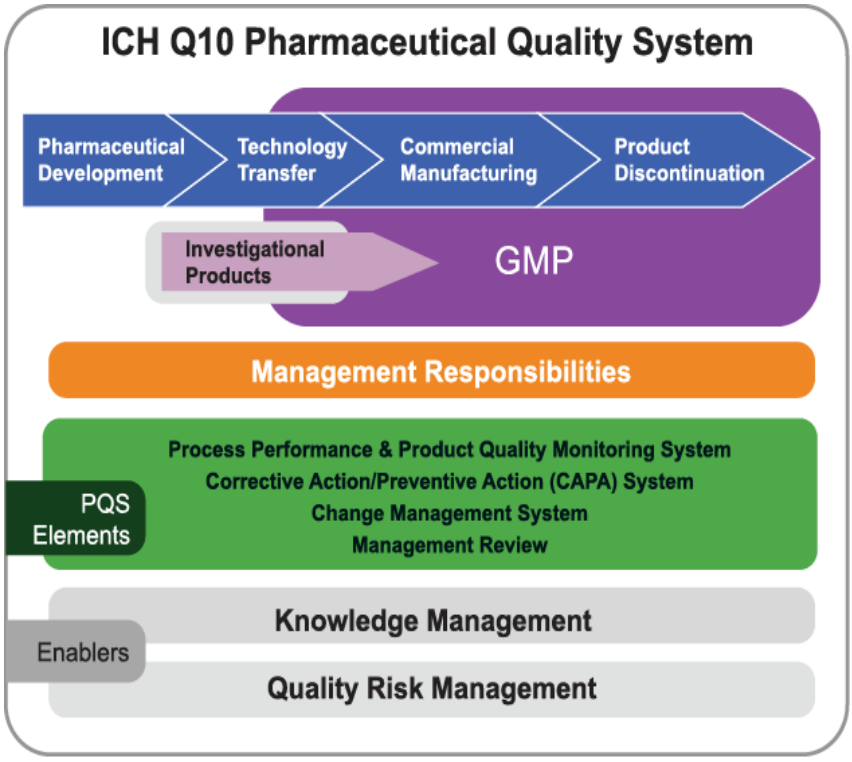

Figure 1.5: Pharmaceutical Quality System per ICH Q10

ICH Q10 clearly stated that:

> *"regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of quality risk management and the effectiveness of the PQS."* (ICH, 2008)

Annex 1 of ICH Q10 described potential opportunities to enhance science and risk-based regulatory approaches. It indicated that demonstration of an:

> *"effective PQS and product and process understanding, including the use of quality risk management principles"* presented an opportunity to *"optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement."* (ICH, 2008)

In spite of ICH Q10 providing a detailed framework for an effective PQS in 2008, over a decade later its vision and value have yet to be realised in the pharmaceutical sector. Continued product recalls, manufacturing, quality and supply chain issues, and increasing drug shortages provide clear evidence that management of risks based on operational knowledge and an effective PQS is still lagging. Evidence of these issues are presented in Chapter Two of this thesis. Mature risk and knowledge bases that are key for making a PQS effective are still in early implementation maturity, as researched

and expounded upon by TU Dublin's Pharmaceutical Regulatory Science Team (PRST researchers) Dr Kelly Waldron (Waldron, 2017) and Dr Ghada Haddad (Haddad, 2019) with respect to QRM, and by Dr Martin Lipa with respect to KM (Lipa, 2021). The researcher asserts that, without effective use of QRM and KM to manage products, processes and systems within the PQS framework, the PQS cannot be effective; and without an effective PQS, it is not possible to optimise PAC processes *"to maximise benefits from continual improvement and innovation"* to quote from ICH Q10. Additionally, until July 2021 (with the publication of the PIC/S Recommendation Paper titled *How to Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management* (PIC/S, 2021)), there was no further practical guidance published on how to demonstrate the effectiveness of a PQS, and this area has remained challenging.

Drug shortages as a 'wicked problem'

A 'wicked problem' is multi-faceted and highly complex and it is explored in more detail in Chapter Two and Chapter Four of this thesis. It offers the possibility of being explored from various perspectives as follows:

- It could be explored for **global regulatory complexity** where the problem is assessed from the lens of different regulatory expectations by country or region, and how these might contribute to the growing challenge of slow and prolonged PAC management.
- It could also be assessed from the perspective of **regulatory authority assessors**, who may not have visibility of a company's PQS, how it is performing, or how its effectiveness is demonstrated and monitored. This likely limits their ability to integrate, in their decision-making, considerations related to the company's latest product and process knowledge or the strength of their PQS in ensuring good risk-based decision-making. These assessors also do not have visibility to how assessors in other countries might have assessed a particular PAC submission; this is of relevance because the assessment of a PAC should be based on science, knowledge and data which does not vary by country.
- Alternately, it could be assessed from the perspective of **regulatory authority inspectors**, who are typically not involved in the review and approval of PACs,

but have visibility into, and an understanding of, how effective a company's PQS is for managing PACs, and how strong (or weak) their KM and QRM systems are.

- It could be assessed for the potential value that would be realised across the pharmaceutical sector if **the interactions and exchange between regulatory assessors and inspectors** were improved, whereby the regulatory oversight is shifted from assessors reviewing each PAC application to inspectors verifying the effectiveness of the PQS in managing PACs.
- It could be assessed from a **pharmaceutical company's** perspective in relation to the challenges encountered and the solutions that the pharmaceutical industry could develop and commit to implementing, even without expecting global regulatory convergence, harmonisation, reliance, or improved interactions between assessors and inspectors.
- It could also be assessed from the perspective of **hospitals and pharmacies** that experience the frontline impact of drug shortages when issues with manufacturing, quality, supply and distribution prevent the availability of medicines. Possibly getting earlier visibility from these stakeholders on potential shortages or weak nodes in their warehouse, distribution and supply networks could contribute to useful solutions
- It could be explored from the perspective of **reforming policies, legislation and legal frameworks** globally to significantly reduce the burden associated with changes and mobilise the pharmaceutical sector towards accelerated continual improvement and innovation. An example of this is the recent work that the European Commission initiated in 2020 to revise the EU variations legislation.
- Finally, and most importantly, this wicked problem could be assessed from the perspective of impact to **patient**, for example, shortage instances where a patient might have to switch to an alternative medicine (where one is available) or even have to go without. Any barrier that impedes the timely and reliable availability of quality medicines, manufactured and tested with state-of-the-art technology, is simply unacceptable.

How do all of the stakeholders who desire to serve and meet the needs of patients, end up in a collective state of dysfunction that detracts from this very objective? Regardless

of the lens that this issue is viewed through, one aspect is certain - all stakeholders involved – pharmaceutical companies, regulators, distributors, policy makers, legislators, healthcare providers, hospitals, and pharmacies - must work together to ensure that patients are never deprived of their medicines. They are the sub-parts of a holistic system that is intended to serve public health needs in the best possible manner.

The researcher made a noteworthy observation during the early stages of this study:

> *not only do these stakeholder groups not work with each other towards collaborative solutions, they also often do not work together within their respective groups to design and implement standard solutions.*

This early insight emerged as a red thread that became increasingly evident and irrefutable as the research study progressed.

Given the enormous breadth of this research topic, framing the problem clearly was challenging, yet essential, in order to develop a defined scope for the research with specific attainable outcomes. It also provided a useful basis for the research hypothesis. These are laid out below in section 1.3.

1.3 Research Hypothesis, Scope, Objectives and Expected Benefits

The research study was developed with the underlying objective:

> ***to accelerate continual improvement and innovation, and reduce global complexity through science and risk-based transformation of PAC management – so that the pharmaceutical sector can ensure the uninterrupted delivery of safe, effective, high-quality medicines to patients.***

Per the problem framing provided in section 1.2, the research hypothesis focused on three core points:

1. The high global regulatory complexity, as described in section 1.2.1, incentivises the pharmaceutical sector to maintain a status quo rather than continually improve and innovate their operations and technologies
2. Without effective use of QRM and KM to manage the lifecycle of products, processes and systems within the PQS, the PQS cannot be effective; and without an effective PQS, it is not possible to *"optimise science and risk-based post-approval change processes to maximise benefits from continual improvement and innovation"* per ICH Q10 Annex 1

3. Without continual improvement and innovation, the pharmaceutical sector cannot sustainably ensure the timely and uninterrupted delivery of high-quality medicines to patients

Although all stakeholders - including regulators, pharmaceutical companies and patients - desire an uninterrupted supply of high-quality medicines and all favour innovation and continual improvement in pharmaceutical manufacturing, these objectives remain unaccomplished, and the problem unsolved. While some progress has been made, it is the researcher's belief that there is still insufficient awareness of and therefore, a lack of mutual understanding and agreement on what the exact problem is. The global nature of the pharmaceutical product supply chain diminishes the value of local regulations that do not address global needs, and the solutions designed by one stakeholder in isolation of their implications for other stakeholders remains ineffective.

This research study explored the implications of global complexity in implementing continual improvement and innovation. It was designed to then use the findings to develop solutions that could be implemented across the global pharmaceutical sector, with the ultimate goal of benefitting patients by ensuring timely and reliable supply of safe, effective, high-quality medicines.

The researcher proposed that science and risk-based applications, utilising the latest product and process knowledge within the framework of an effective PQS to assess individual PACs, could enable companies to overcome existing barriers to proactive continual improvement and innovation. It was postulated that this, in turn, should help reduce potential drug shortages in the global environment. It was proposed throughout this study that in order to realise the regulatory flexibility envisioned in ICH Q10, Annex 1, any PAC that could be demonstrated via a current knowledge-based risk assessment to reduce risk to patients should be implemented immediately within the structure of an effective PQS, and without requiring prior-approval. This approach fully recognises the need for regulators to maintain their oversight of how pharmaceutical companies manage such PACs; such oversight is already provided for via the GMP inspection and market surveillance programs that regulators throughout the world currently operate. The oversight would simply shift from the assessors to the inspectors,

At the outset of this research, there was no guidance available on what constitutes an effective PQS or how might a pharmaceutical company demonstrate the effectiveness of its PQS for the management of PACs. This research, therefore, also explored how to demonstrate effective management of PACs within the PQS.

The study also sought to explore how to enable alignment, common understanding and mutual appreciation between regulators and the pharmaceutical industry of the challenges they each encounter in effective PAC management. This was essential to activate collaborative discussions and the development of standard practical solutions that could be deemed acceptable by both stakeholder communities. It was also anticipated that such standard solutions, when implemented, would instil confidence among regulators in a company's ability to effectively manage and implement PACs within the framework of their PQS, without the need for prior regulatory approval.

Furthermore, it was envisaged that the results produced from this research and its jointly designed practical solutions could be transformational in facilitating the availability of medicines and catalysing technical innovation in the pharmaceutical sector, while also facilitating the following outcomes and benefits:

- Reducing the burden for both pharmaceutical companies and regulators by
    - Enabling faster and more timely implementation of knowledge
    - Simplifying product supply and inventory logistics due to PACs
    - Enabling regulators to focus their resources on high impact, high value activities while deprioritising low risk PACs, based on sound product and process understanding, robust QRM, KM, and an effective PQS
- Developing standard solutions that facilitate harmonisation globally across the pharmaceutical industry and which lead to increased harmonisation across regulatory agencies
- Reducing the time lag between when new knowledge is gained during the commercial life of a product and when it is actually implemented to drive continual improvement
- Building trust with regulatory agencies that can ultimately provide powerful mechanisms and incentives for both pharmaceutical companies and regulators to

downgrade PACs from prior-approval to notification, or even simply to manage them only within the PQS

- Ensuring patients receive value from the best innovations in a timely manner

The overall outcome of this research is a set of methodologies and practical standard solutions which can facilitate a transformational shift in PAC implementation timelines and a significant reduction in PACs requiring prior-approval.

1.4 Why an Overarching Framework of a PQS, QRM, and KM?

It must be noted that pharmaceutical companies cannot decide the regulatory outcomes for individual PACs – this is the responsibility of regulatory authorities. At the same time, regulators cannot decide on the innovation and continual improvement decisions that companies must make based on their evolving product and process knowledge. The pharmaceutical industry also cannot create mutual reliance between regulatory authorities or reduce the complexity of the global regulatory landscape. Even so, the concept of mutual regulatory reliance started to emerge as a topic of substantive relevance during the course of this research. Mutual reliance in a PAC context means that, when one regulatory authority has assessed a PAC or a company's PQS, other regulatory authorities may rely on and accept their conclusions (and approval or rejection) of a company's PAC. This would speed up the approval timelines for PACs, improve consistency in approval decisions across countries, and save resources both for companies and regulators by eliminating redundancies in PAC reviews and approvals.

The World Health Organisation (WHO) is a United Nations agency that connects nations, partners and people to promote health, keep the world safe and serve the vulnerable – so everyone, everywhere can attain the highest level of health. The WHO, through its Working Document QAS/20.851, *Good Reliance Practices in Regulatory Decision-Making: High Level Principles and Recommendations* (WHO, 2020), has in recent years been encouraging reliance between regulatory authorities; however, the desired state is still far from realisation. Solutions that enable mutual reliance and reduce regulatory complexity are still needed; however, these are not directly within the scope of this research study, which is focused specifically on science and risk-based

solutions that pharmaceutical companies can implement to support management of additional PACs within their PQS.

These aspects related to the role of assessors in evaluating a PAC versus inspectors in evaluating a company's PQS for, especially change management. This is a topic that is both within and also outside the sphere of control of a pharmaceutical company, and while PACs may have a local scope, there can also be international interaction opportunities for regulatory authorities with regard to those same PACs. This is illustrated in Figure 1.6 below as developed by the researcher:

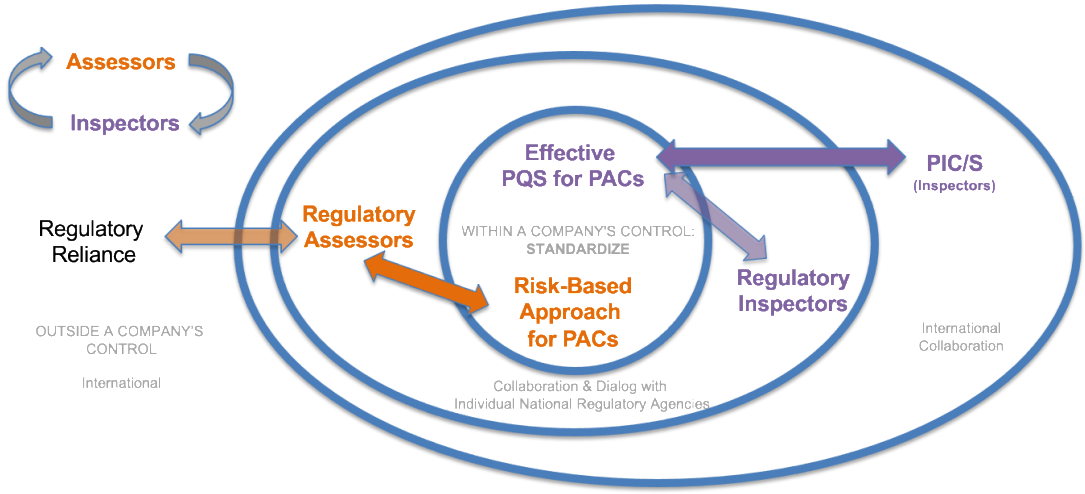

Figure 1.6: Roles and Interactions for Regulatory Authorities and Pharmaceutical Companies

As laid out in the research hypothesis in section 1.3 and as envisaged by ICH Q10 Annex 1, sound science and risk bases (i.e., mature QRM), utilisation of the latest product and process knowledge (i.e., mature KM), and an effective PQS are anchors to maximise continual improvement and innovation. The responsibility of developing methodologies and solutions which demonstrate effective QRM per ICH Q9, *Quality Risk Management* (ICH, 2005c), KM, and an overall PQS that is capable of effectively managing PACs, must start with pharmaceutical companies as a first step. This could then be followed by exchanges with regulators to build trust in the solutions proposed by the pharmaceutical industry, as well as increased transparency from regulatory assessors to companies with regard to their decision-making criteria and processes for PAC assessments. It could eventually result in opportunities for assessors to provide increased transparency to each other with regard to their PAC assessment work and

their decision-making, to help drive regulatory convergence, mutual reliance and a reduction of global regulatory complexity.

This research therefore probed into appraising where and how QRM and KM applications could be implemented for PAC management and how one could demonstrate the capability of the PQS in effectively managing PACs, such that prior-approval by individual regulatory authorities would be necessary only for higher risk changes. This research also intended to translate high-level concepts and guidance in this area into practical, standardised, implementable solutions.

The product and process knowledge that a company gains during the commercial life of a product continues to grow throughout the product's life. A company's PQS should provide a structured framework to capture and manage such growing knowledge. At the same time, the QRM system employed by the company should enable the utilisation of this knowledge to drive risk reduction and continual improvement. It is not always possible to update product filings with the latest knowledge in as timely a manner as is possible to update and maintain that knowledge within the company's PQS. This creates a lag in the knowledge for a product that resides within the company's PQS versus what is documented and registered in product filings with regulatory authorities, as illustrated in Figure 1.7, developed by the researcher:

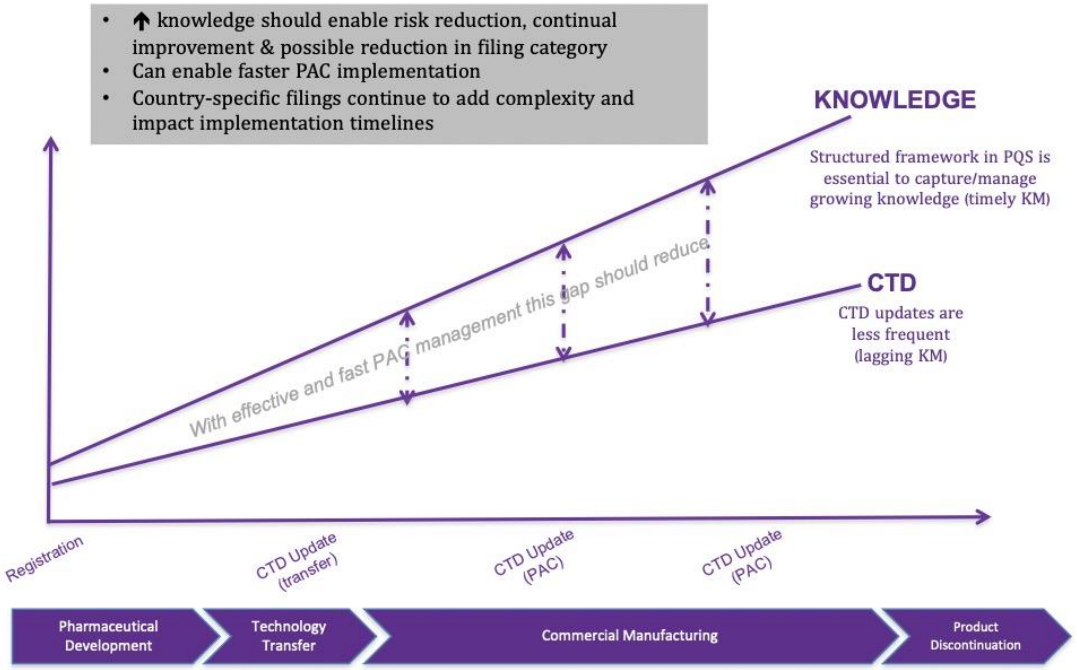

Figure 1.7: Managing Product Knowledge in the PQS vs. Regulatory Filings

This results in a missed opportunity for regulatory authority assessors to utilise the latest product and process knowledge while making their PAC regulatory categorisation and approval decisions.

The research hypothesis propounds that QRM could provide a desired framework that utilises the latest product and process knowledge (which is captured in the company's PQS) to identify, assess and adequately control risks associated with a proposed PAC, such that PACs presenting a lower risk to product quality and/or patient safety relative to the current state could be managed within the PQS or as notifications to regulatory authorities, without requiring regulatory approval prior to implementation of the change. Figure 1.8, developed by the researcher, illustrates such a framework – one that is based on QRM and KM within the construct of an effective PQS, and is consistent with the expectations of ICH Q10.

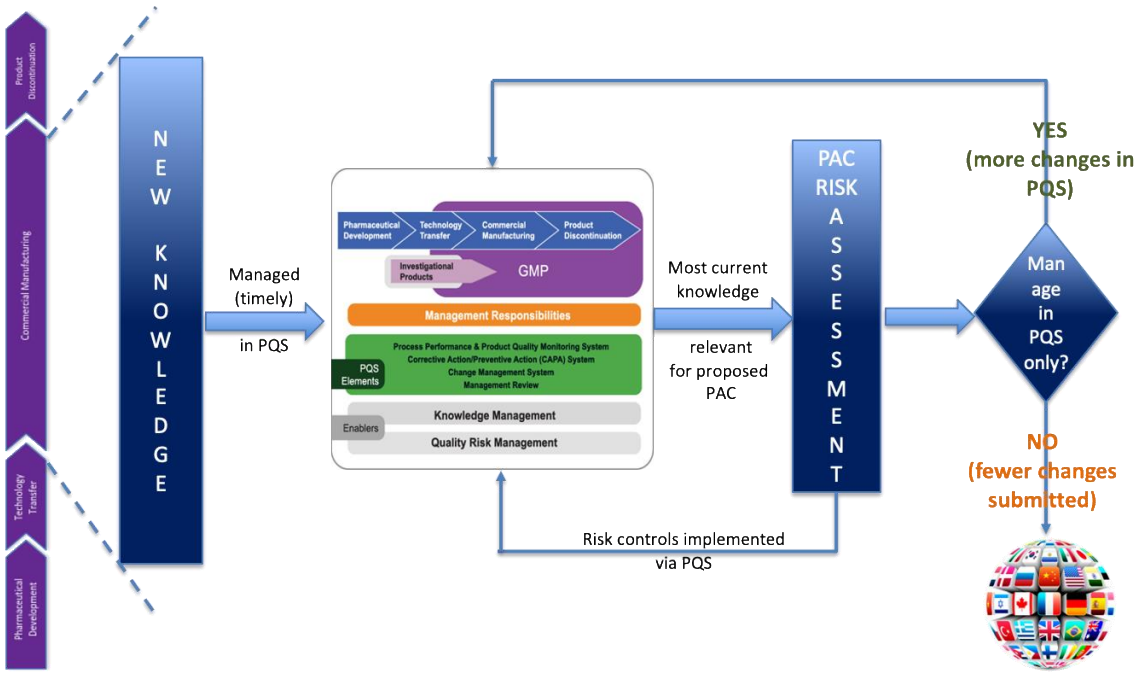

Figure 1.8: QRM and KM as Enablers for Effective Management of PACs in the PQS

Reading the figure left to right, new knowledge that is acquired during the commercial life of a product should get documented within the PQS. When a PAC is needed, the latest knowledge relevant to that PAC, as captured within the company's PQS, should be utilised to perform a risk assessment on the PAC. The needed controls identified in the risk assessment should be implemented through the PQS. The risk level of a PAC identified by the risk assessment should help answer the question: *'Can the change be managed within the PQS only'*? If yes, then the change should not require a regulatory prior-approval submission, and instead regulatory oversight will transfer to the inspector when inspecting the PQS. If no, then the change must be submitted to regulatory authorities for assessor review and prior-approval.

This research claims that application of such an approach could reduce the number of PACs that need prior-approval regulatory submission. To facilitate this the *1VQ for PAC Initiative* developed standard science and risk-based solutions during 2019-2021 that companies could apply to facilitate management of more PACs within the PQS; at the same time, the solutions provided standards for inspectors to audit the PQS against. The impact and level of reduction that could be achieved by applying the standard solutions resulting directly from this research, and those identified as additional

opportunities, are discussed later in Chapter Ten, section 10.3 of this thesis, and depicted in Figure 10.1.

Returning to the premise at the centre of this study, patients deserve to receive every dose of every medicine they need, every single day. They place their trust in regulators and pharmaceutical companies for reliable supply of safe, effective, high-quality medicines. This research led to the proposal of a clear and practical path to realise the promise of ICH Q10 and maximise benefits for patients, depicted in Figure 1.9 below as:

1. **Current state as starting point:** risk for a PAC remains the same, yet there are different submission requirements and approval timelines across different countries and regions
2. **As a first improvement milestone:** companies consistently start performing risk assessments for individual PACs, utilising the latest product and process knowledge relevant for those PACs
3. **As the next improvement milestone:** risk-based decision-making by regulators takes into account the company-specific product and process knowledge and effectiveness of their PQS to acceptably manage PACs without extensive regulatory approvals, leading to reduced reporting category for PACs that do not increase risk to product quality or safety
4. **The final milestone:** consistency in risk-based decision making for PACs across countries and regions, with convergence and eventually reliance, all resulting in faster global implementation of PACs

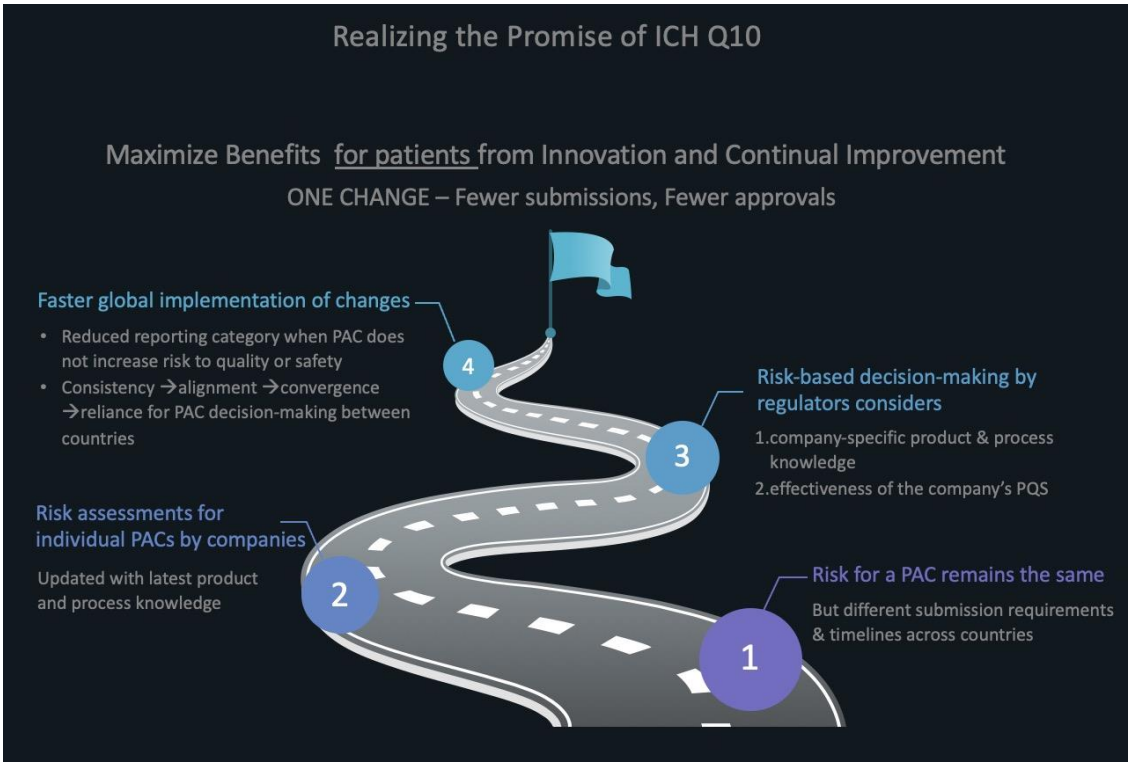

Figure 1.9: Realising the Promise of ICH Q10 for Patients

1.5 Overall Research Progression, Outcomes and Timelines

Though this thesis is laid out in six distinct parts, these were not sequential in the order they were executed, but rather iterative with several components being interconnected and occurring in parallel. The approach taken for the study was necessary in order to gather input, develop a position or a draft solution, solicit feedback from multiple stakeholder communities through various focus groups, interviews, conference presentations or discussion sessions, adjudicate and incorporate such input, update and re-socialise for ratification or endorsement prior to publishing as a standard solution. While it is acknowledged that solving 'wicked problems' requires collaborations across various stakeholders and that no one stakeholder group can singularly resolve such complex issues, Figure 1.10 summarises the specific contributions the researcher made towards addressing this 'wicked problem' and the high-level study timeline:

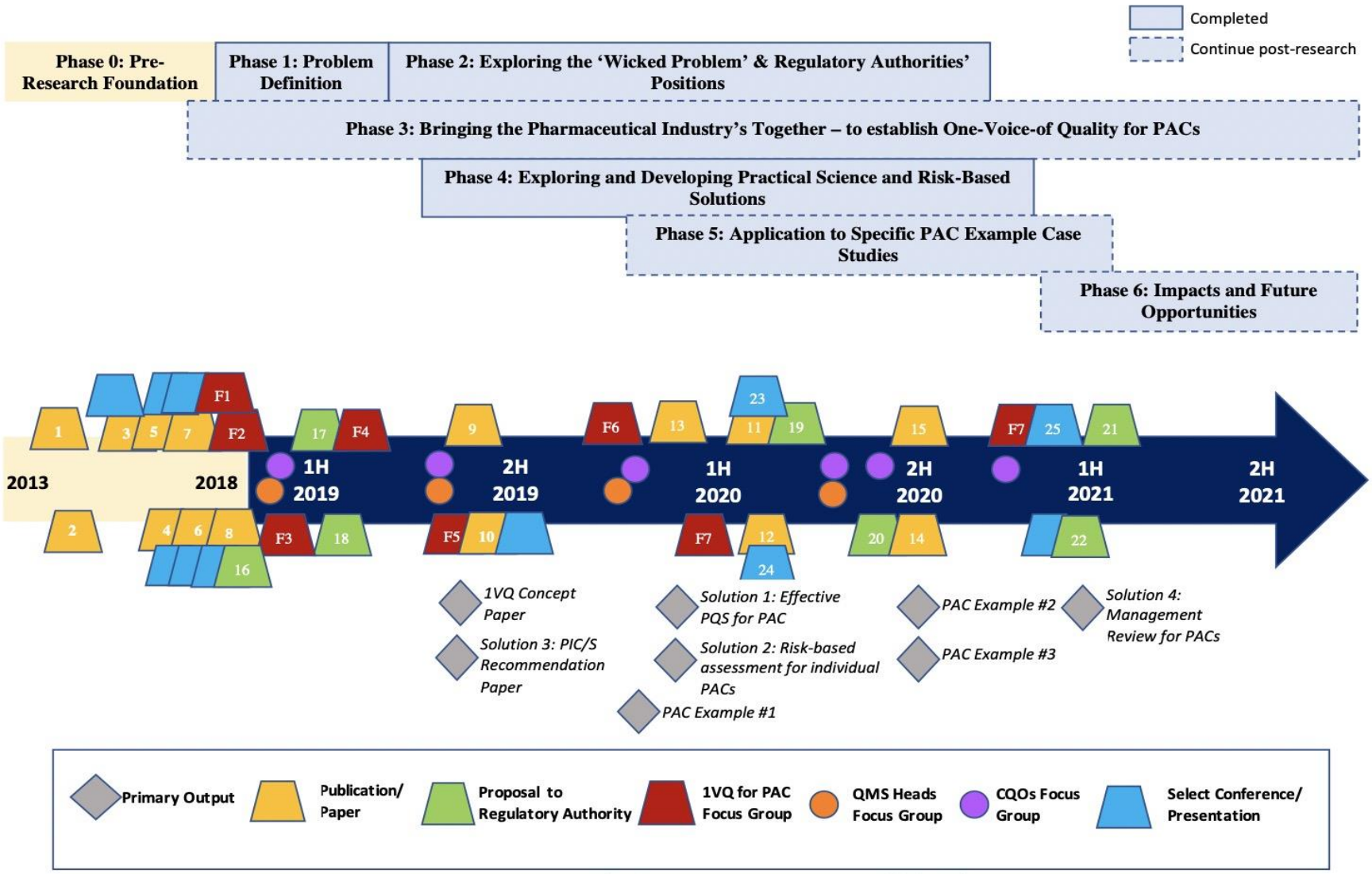

Figure 1.10: Research Outputs Progression and Timelines

For each of the activities numbered in Figure 1.10, the papers published and proposals submitted to regulatory authorities are supplied.

- The pre-research publications that were foundational for this research are discussed in Chapter Five and Chapter Seven of this thesis
- The publications resulting from this research are discussed in Chapter Eight of this thesis
- Specific proposals and contributions made to various regulatory authorities are discussed in Chapter Six of this thesis.

This chapter has introduced the research study, its context and background, framed the problem being addressed, and outlined the key contributions from the researcher in terms of inputs into, and outputs from, this research study.

The next chapter provides the literature review conducted in order to explore published data and insights of relevance for this study.

Chapter Two

Literature Review

Throughout the research study a literature search and review on the topics of global regulatory complexity, PAC management, and product lifecycle management, in addition to drug shortages, QRM, KM and PQS within the pharmaceutical sector was carried out. Additionally, the researcher wished to understand foundational elements of Quality Systems that are relevant to any customer-oriented industry. Therefore, characteristics of a QMS per the ISO 9000 series quality systems framework, which is applicable to a broad range of industries beyond the pharmaceutical industry, and which actually formed the basis for the ICH Q10 PQS model were also reviewed. Though there are other examples of 'wicked problems', such as climate change, poverty, world hunger, etc., the review of this topic focused on a seminal paper in 1973 by Rittel and Weber (Rittel and Webber, 1973), because it describes characteristics that are relevant for any 'wicked problem'. Beyond this seminal paper; a deep literature review into other 'wicked problems' was not deemed necessary for this study, given the highly unique nature of each wicked problem and the very restrictive (if any) ability to draw common lessons or parallelisms in solving them.

The literature search also revealed some deficiencies, in that there is very little published on global pharmaceutical regulatory complexity, PAC management or their linkage to drug shortages. This lack of literature did not come as a surprise to the researcher and further confirmed the need for this research. Some literature found on these topics was published by other stakeholders such as the Economist Intelligence Unit (EIU), which is reviewed in Chapter Four of this thesis, but not much by the pharmaceutical industry. Thus far, there is also no published guidance for assessors on how to perform PAC assessments; and until publication of a recent PIC/S guidance in July 2021 (PIC/S, 2021), there has been limited to no guidance for the pharmaceutical industry or inspectors on how to demonstrate or assess effectiveness of a PQS specifically for PACs. Indeed, much of the published literature directly relating to the global pharmaceutical regulatory complexity and PAC management was driven by the

researcher, either prior to or during the course of this study, and as such the researcher cites this work throughout the thesis.

Figure 2.1 lays out in broad heading the topics for which literature was reviewed, and it includes a mapping of the applicable thesis chapters or sections where they are discussed. The colour-coding shown in the figure indicates whether the literature reviewed was specific to the pharmaceutical sector, whether it applied to other industries, or whether it was applicable to even larger problems related to social policy or public good.

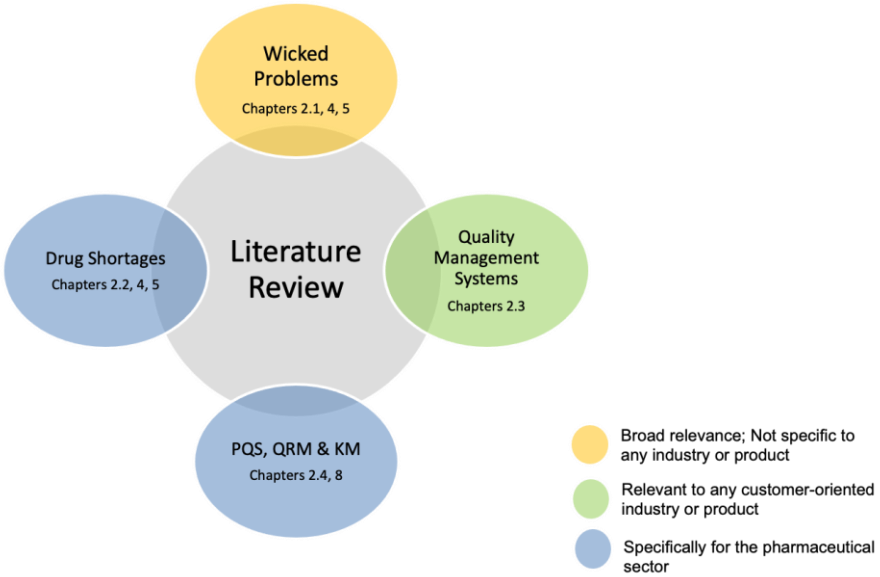

Figure 2.1: Scope of Literature Review

While the body of guidance and published literature is rich on risk management in other industries, as well as on QRM in the pharmaceutical sector, and on QMSs in general, it was found that not much has been published on linking enhanced science and risk-based approaches to PAC management beyond ICH Q10, *Pharmaceutical Quality System* (ICH, 2008), ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (ICH, 2019), and the researcher's prior and current body of work (described throughout this thesis).

It was also found that extensive published literature exists for KM in other industries, but it is far less for the pharmaceutical sector, especially when compared to QRM literature. There is even less published on the practical application of enhanced science

and risk-based approaches for high complexity, multi-faceted topics such as drug shortages, and on the resulting expected optimisation of regulatory approaches to enable continual improvement and innovation within the pharmaceutical industry.

Recent PRST doctoral theses from Dr Martin Lipa (Lipa, 2021) and Dr Paige Kane (Kane, 2018) provide thorough reviews of the published literature on knowledge management. Similarly, the PRST doctoral theses from Dr Ghada Haddad (Haddad, 2019), Dr Kelly Waldron (Waldron, 2017), and Dr Kevin O'Donnell (O'Donnell, 2007) provide detailed literature reviews on QRM in the pharmaceutical sector. Though conducted over a decade ago, the comprehensive literature review of risk management by Dr O'Donnell is noteworthy, as it covers risk management in the aeronautics and nuclear power generation industries and compares it to practice in the pharmaceutical industry. Finally Dr Nuala Calnan's doctoral thesis (Calnan, 2014) focused on a review of ICH Q8, Q9, Q10 and Q11, with an emphasis on QMSs and the importance of shifting from compliance-based quality to excellence-based quality. In lieu of conducting another independent literature review into QRM and KM, the researcher opted to review the insights from these PRST doctoral theses and build upon them.

This review was supplemented by the researcher's 10+ years of deep practical first-hand experience with QRM and KM as part of her pharmaceutical industry affiliation and work. Figures 2.2 and 2.3 below depict key aspects of the researcher's career, leadership, training and influencing experience in the pharmaceutical sector. It includes her role and involvement in establishing a QRM program at her company of employment, her activities in training and advancing risk-based application both for the company and broader for the pharmaceutical sector, leading up to her pre-study work on drug shortages and eventually this research study into PAC management; further details on the researcher's prior-experience are provided in Appendix I of this thesis.

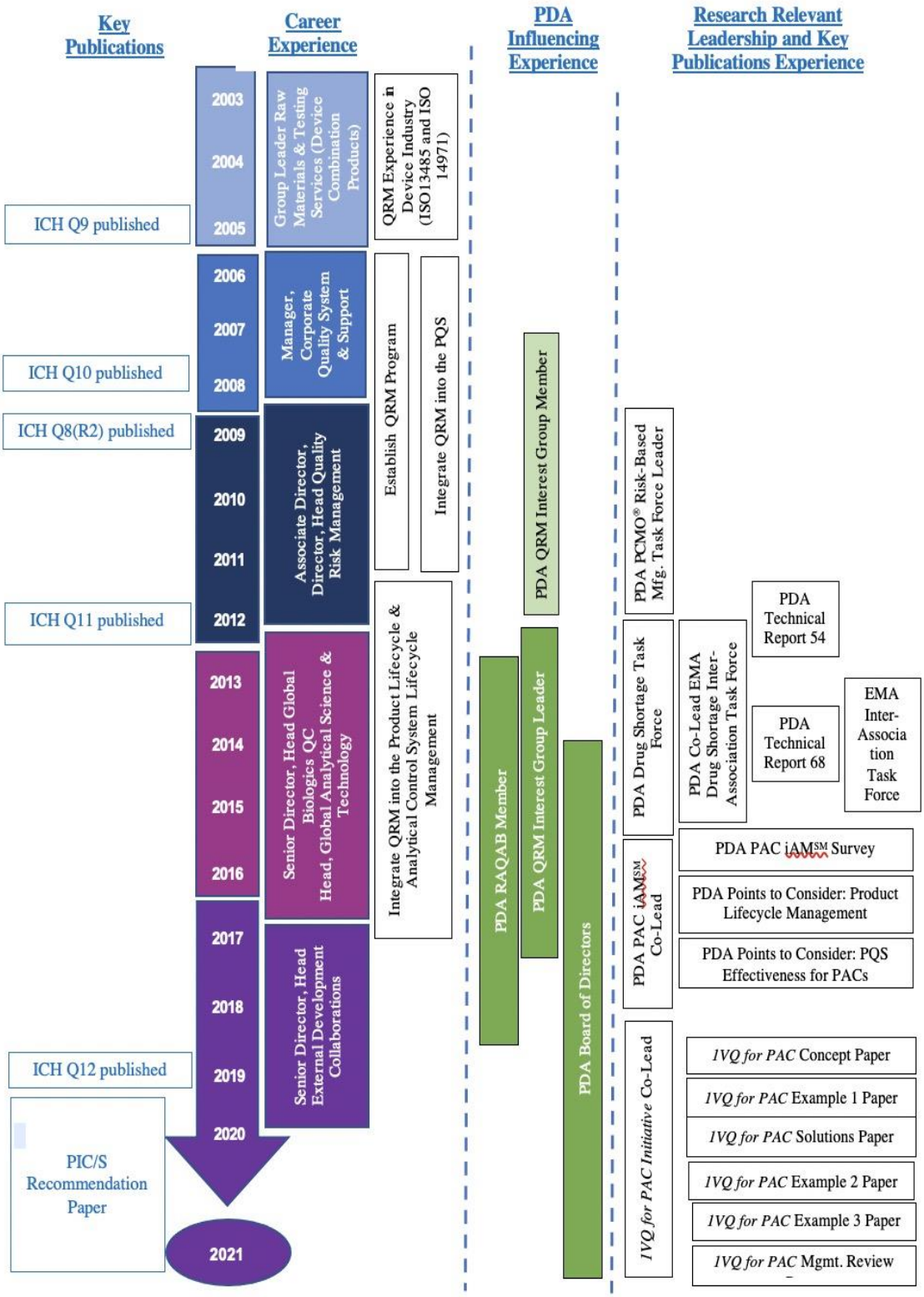

Figure 2.2: Summary of Researcher's Career, Leadership and Influencing Experience

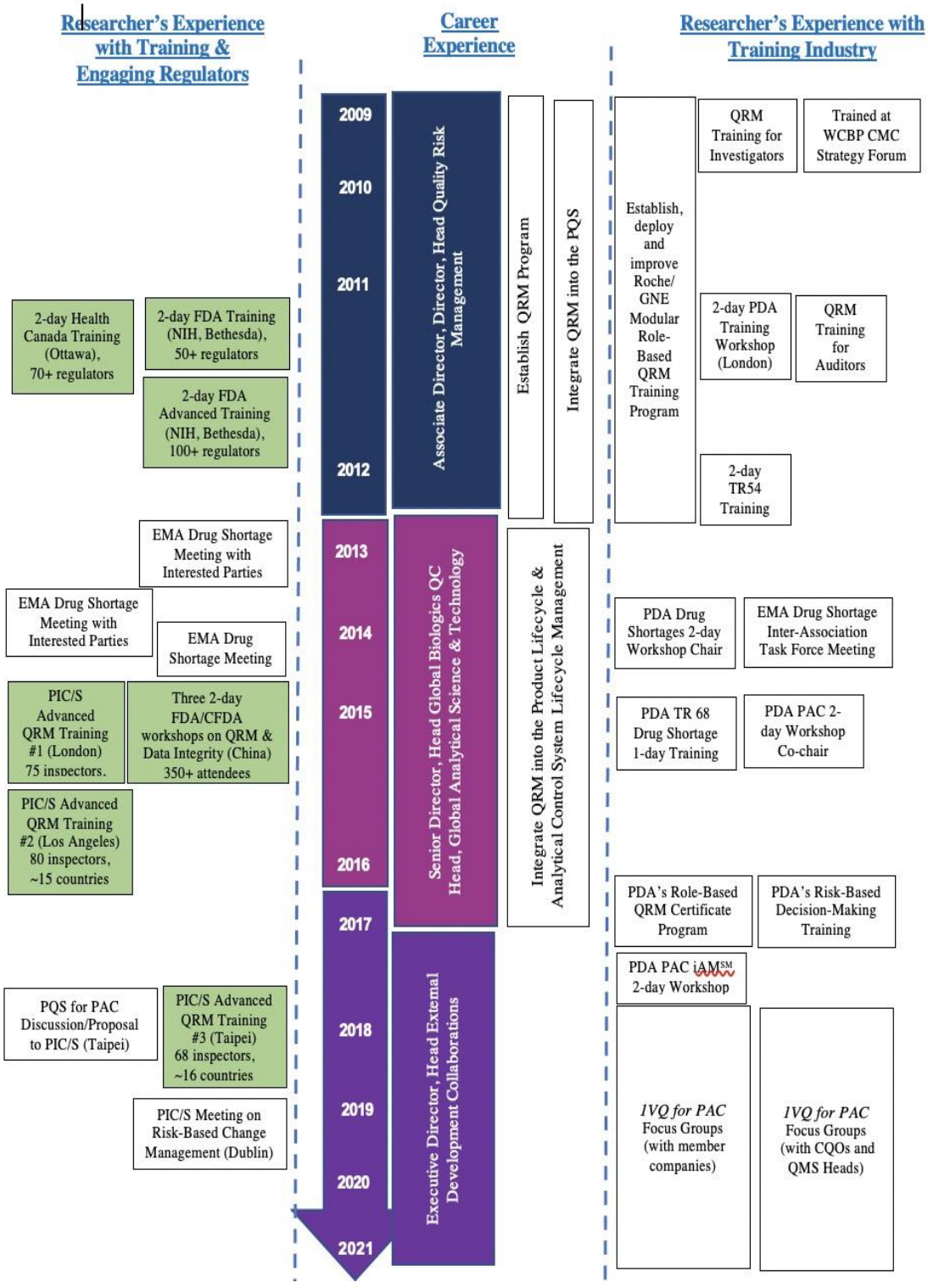

Figure 2.3: Researcher's Experience with Training Regulators and the Pharmaceutical Industry

The literature review for this research focused on a review of QMSs in a broader context beyond the pharmaceutical sector, literature relevant to describing the global regulatory landscape in the context of drug shortages, and the application of enhanced science and risk-based approaches to PAC management**. Given that the literature on these topics was more finite, and to allow for more integrative understanding, topic-specific literature reviews are embedded within the specific chapters of this thesis as per Figure 2.1 above.** A general overview of literature on QMSs and applicable ICH guidelines that form the basis of this research are provided in this chapter, with topic-specific aspects integrated into other relevant chapters.

Furthermore, it is useful to provide a brief overview and context of the pharmaceutical sector relevant for this research. For the scope of this study, the term 'pharmaceutical sector' is comprised of three primary stakeholders - *pharmaceutical industry*, *regulatory agencies* (regulatory authorities that have legal authority to regulate the pharmaceutical industry in their respective countries) and *academia* (where direct collaborations with the pharmaceutical industry or regulators enable advancement of patient-focused work). The pharmaceutical sector landscape, with key enterprises that participated in, contributed to, and are referenced throughout this research study, is depicted in Figure 2.4 (modified with permission from the original figure developed by Dr Martin Lipa for PRST (PRST, 2021). The figure serves as a useful 'quick reference guide' to these entities as mentioned throughout this thesis.

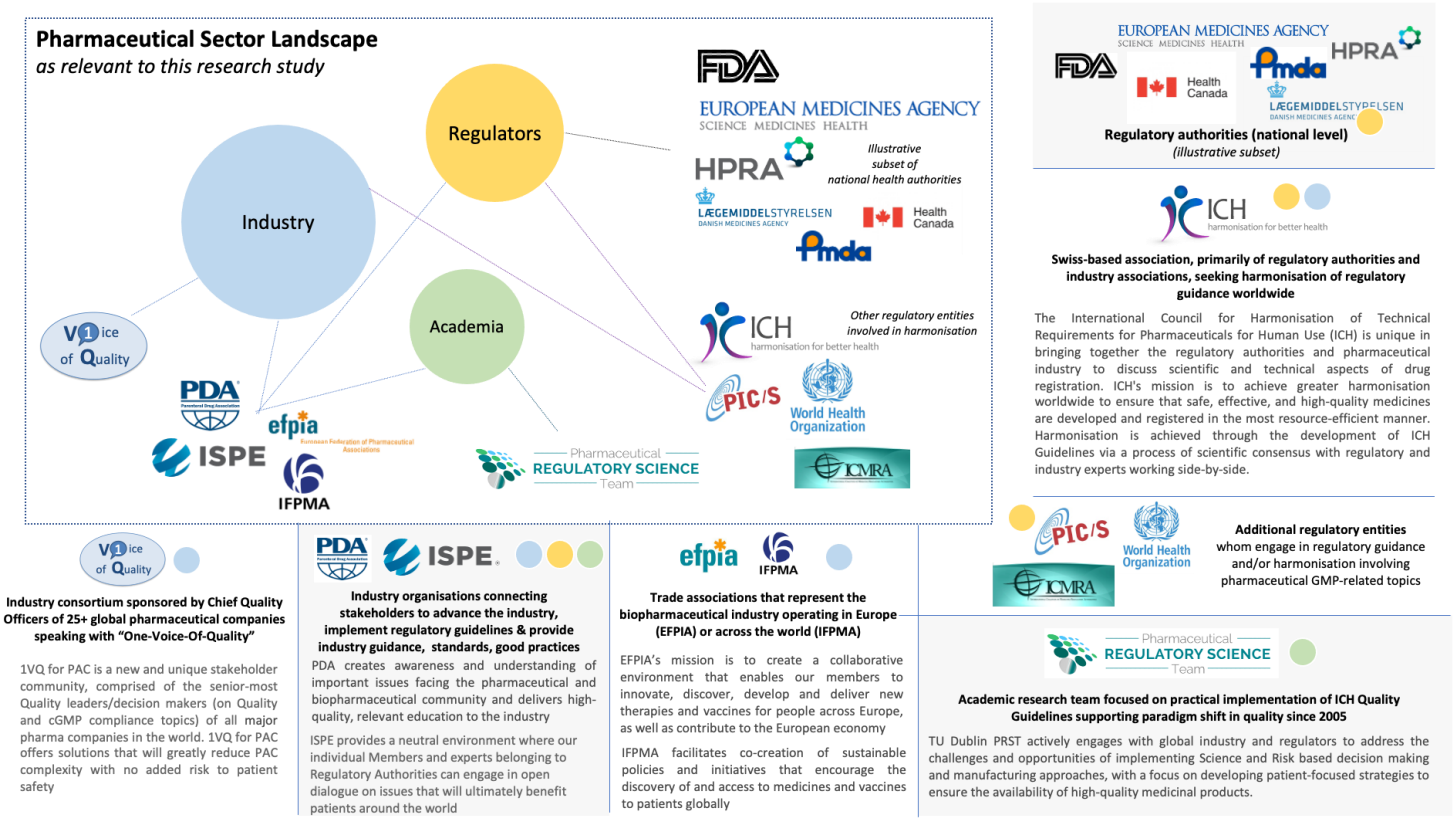

Figure 2.4: Pharmaceutical Sector Landscape Relevant for Research[4]

[4] Descriptions for *1VQ for PAC*, PDA, ISPE, EFPIA, IFPMA, PRST and ICH, are taken from their respective *About* pages (*1VQ*, 2021; EFPIA, 2021; ICH, 2021; IFPMA, 2021; ISPE, 2021; PDA, 2021; PRST, 2021)

As a large part of this research study is based on ICH guidelines, it is useful to provide a brief overview of ICH. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is an international non-profit association that brings together regulatory authorities and the pharmaceutical industry to:

> "*achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner*" (ICH, 2021).

ICH brings experts from regulatory authorities and industry together to develop guidelines through a process of scientific consensus. ICH guidelines fall in the following four categories (ICH, 2021):

1. ***Quality (Q):*** *"Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management."*
2. ***Safety (S):*** *"ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years."*
3. ***Efficacy (E):*** *"The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines."*
4. ***Multi-disciplinary (M):*** *"Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI)."*

The order of literature review presented in the sections below, starts with the topic broadest in scope i.e., wicked problems, and progresses to more specific topics with direct implications for this study as follows:

- Wicked Problems
- Drug Shortages
- Quality Management Systems
- ICH Q10, *Pharmaceutical Quality System*
- ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*

It is noteworthy that throughout the literature review, the importance and relevance of global considerations provided a useful basis given the global nature and implications of this research topic.

2.1 Wicked Problems

A 'wicked problem' was defined in the literature for the first time in 1973, by Rittel and Webber as '*a problem highly resistant to solutions*' (Rittel and Webber, 1973). They identified that wicked problems are highly complex, stubborn problems that cannot be well-defined, do not have easily defined solutions, and cannot be solved by any one group of people. Addressing wicked problems must be based on *systems thinking*, seeking to answer two primary questions within the context of ever-evolving social complexities – "What *do* the systems do?" and "What *should* these systems do?". The concept of *systems thinking* and its relevance and application for this research study is expanded upon in Chapter Three, section 3.2.1 of this thesis. Examples of wicked problems include climate change, obesity, poverty, hunger, sustainability and, biodiversity loss. Rittel and Webber stated that:

> "*one of the most intractable problems is that of defining problems (of knowing what distinguishes an observed condition from a desired condition) and of locating problems (finding where in the complex causal networks the trouble really lies). In turn, and equally intractable, is the problem of identifying the actions that might effectively narrow the gap between what-is and what-ought-to-be.*" (Rittel and Webber, 1973)

This statement essentially summaries the core challenge of this research topic. As described in Chapter One, section 1.2 of this thesis, the task of framing the problem, its scope, the research hypothesis, and exploring possible solutions, was not a simple undertaking. Not only is the gap between *what-is* and *what-ought-to-be* difficult to articulate, equally - if not more difficult - is the task of conclusively determining whether or not a set of solutions has narrowed that gap. Considering the findings from this research, this aspect of the 'wicked problem' has been expounded upon in the concluding Chapter Ten of this thesis.

Rittel and Webber identified ten features that are characteristic of all 'wicked problems', irrespective of how diverse and distinct they might be from each other. The researcher developed Figure 2.5 below for a visual depiction of these characteristics.

Figure 2.5: Characteristics of a Wicked Problem (Rittel and Webber, 1973)

Some parties have identified the COVID-19 pandemic as a 'wicked problem' (Kerr and Glantz, 2020), since it is presenting many of the typical characteristics and societal complexities. This may be proved to be the case, but given that vaccines have been bending the curve and the world is still in a state of pandemic, it might be too soon to conclude this.

In 2016, Vinther asserted that drug shortage is a 'wicked problem', because it presents all the characteristics of a 'wicked problem' as outlined by Rittel and Webber (Vinther, 2016). Chapter Four, section 4.1of this thesis specifically discusses why drug shortage can be considered a 'wicked problem'.

2.2 Drug Shortages

Chapter One of this thesis framed the problem and laid out the hypothesis that there is a connection between drug shortages and inadequate continual improvement and innovation due to the global complexity for PAC management, even if a direct correlation is difficult to make. There is an extensive body of information and data published on drug shortages, including each country having their own database for the tracking and notification of drug shortages. For the purpose and scope of this research, it wasn't deemed necessary to do a detailed literature review on drug shortages broadly, but rather a targeted search was performed to find any literature published linking drug shortages to slow innovation or global regulatory complexity.

Most literature on drug shortages centres on it being a multi-causal issue, with the causes ranging across a wide variety of economic, business and manufacturing or supply chain factors as shown in Figure 2.6 (Birgli®, 2013).

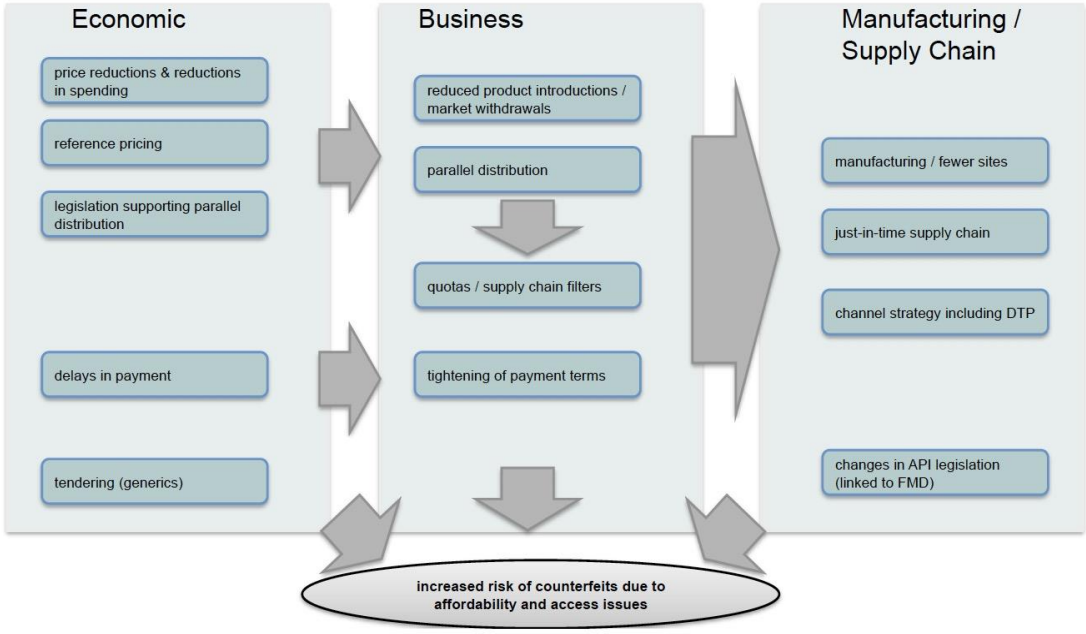

Figure 2.6: An overview of the Causes of Drug Shortages (Birgli®, 2013)

Regulators such as the European Medicines Agency (EMA) and FDA have identified manufacturing or product quality issues as a prominent cause of drug shortages; one example of this is given in FDA's 2019 Drug Shortages Report, which shows that 62% of shortages between 2013-2017 were as a result of manufacturing or quality issues

(EMA, 2012; FDA, 2019). The researcher contends after applying the *Five Whys* technique, as described in Chapter One, section 1.2.2 of this thesis, that the inability to make changes (to fix issues) due to the global complexity, is as an appreciable disincentivising factor.

Researcher's Prior-Work on Drug Shortages: Resulting in the Publication of PDA Technical Report 68

Prior to initiating this research study, the researcher identified that taking a science and risk-based approach was necessary to address drug shortages. In 2012, the researcher was instrumental in forming and leading a PDA Drug Shortage Task Force. The researcher chartered and set up the Task Force, identified suitable participants comprising of industry experts and regulators, and held multiple working sessions to develop the scope, objectives and deliverables of the Task Force. The Task Force comprised of seven experienced members drawn from the pharmaceutical companies and regulatory agency listed in Table 2.1 below:

Table 2.1: Composition of PDA Drug Shortage Task Force

Participants
Amgen
Concordia ValSource
G-CON Inc.
Genentech
Health Products Regulatory Authority (HPRA)
Merck Sharp & Dohme
Sanofi Pasteur

The Task Force met regularly over 18 months with a view to developing strategies for managing drug shortages. These concepts, strategies and a Risk Triage model for drug shortages were published by PDA in 2014 as Technical Report 68, *Risk-Based Approach for Prevention and Management of Drug Shortages* (Ramnarine *et al.*, 2014). This work initiated a review into how aging facilities and equipment could result in manufacturing and quality issues which could then lead to drug shortages. The research explored barriers that pharmaceutical companies encounter in proposing and making

changes to upgrade aging facilities, equipment, methods and processes. A specific barrier that the researcher identified during the course of this pre-research study was the global regulatory complexity that is associated with implementing PACs. The researcher found that this barrier created a disincentive for pharmaceutical companies and prevented them from implementing the latest technology or making continual improvements that could in fact reduce manufacturing and quality issues, and ultimately prevent resulting drug shortages. The researcher identified an interesting paradox:

> *while continual improvement and innovation could reduce risk to drug shortages, the enormous global complexity with PAC management delays resolution of compliance or quality issues and continual improvement to such an extent, that it potentially contributes to exacerbating the issue of drug shortages*.

Though published as a PDA Technical Report and as work conducted by the Task Force, the thought leadership and core concepts including the Risk Triage model and the Drug Shortage Prevention and Response Plan were original contributions from the researcher.

This prior work by the researcher on risk-based application for drug shortages was instrumental in instigating this research study, and as such will be referred to throughout this thesis; details of Technical Report 68 are described in Chapter Five, section 5.3.4 of this thesis. For ease of reading, it will be referred to as PDA Technical Report 68 hereon, and a citation is not deemed necessary for each reference instance in this thesis.

Regulators' Focus on Drug Shortages

The FDA in 2019 published a report on drug shortages (that was updated in 2020) on root causes and potential solutions (FDA, 2019). It identified economic forces as the overarching root cause. The report also found three additional major root causes:

1. Lack of incentives to produce less profitable drugs
2. Market does not recognise and reward manufacturers for mature Quality Management Systems
3. Logistical and regulatory challenges make it difficult for the market to recover after a disruption

Root causes #2 and #3 are directly relevant to this research. This FDA report was the first time that a regulatory authority had acknowledged the link between the regulatory complexity and a lack of utilising an effective PQS to prevent shortages.

The report identified regulatory complexity being a factor contributing to drug shortages, specifically stating:

> "*Many drug manufacturers supplying the U.S. market are in fact global operations that also supply other regions. Making post-approval changes to update manufacturing operations generally requires that they seek approval not only from FDA but the regulators in the other markets.* ***According to industry observers, many post-approval changes to regulatory filings require prior-approval by the regulatory authority of every country individually, and this can be over 100 countries for globally marketed products. The global approvals for changes can often take years because of varying requirements and timelines across different regulatory authorities, and this creates disincentives for timely improvements to manufacturing operations that could reduce the risk of drug shortages***." (FDA, 2019)

The bold text regarding discussion with industry observers reflected precisely the dialogue the researcher and Vinther had had with FDA in January 2019, that is discussed in Chapter Six, section 6.1.2 of this thesis, indicating their direct impact and influence on this report.

The report's recommendations to address the second and third root causes were to:

- Create a rating system to incentivise drug manufacturers to invest in achieving Quality Management System maturity
- Promote sustainable private sector contracts – whereby contracting practices by payers, purchasers and global purchasing organisations (GPOs) recognised and rewarded manufacturers for mature quality management

In addition to the recommendations, the report also identified several FDA initiatives to prevent and mitigate shortages, with one of them being the adoption and implementation of ICH Q12 (FDA, 2019).

The EMA has also undertaken extensive activities as described in Chapter Five, sections 5.2.1, 5.3.1, 5.3.3 and 5.3.5 to address drug shortages; however, these have not drawn any linkages between global regulatory complexity or PAC management and drug shortages. Therefore, they are not included as part of literature review in this chapter.

Part Two of this thesis, Chapter Four and Chapter Five further delve into specific responses and literature from various regulatory authorities (FDA, EMA, WHO) and the pharmaceutical industry on drug shortages within the context of this study.

2.3 Quality Management Systems, ISO 9001:2015 – Basis for the Pharmaceutical Quality System

Having focused on the 'wicked problem' and how drug shortages can be classified as such, with one cause of them being manufacturing and quality issues, this section reviews literature pertinent to QMSs.

ISO is an independent, non-governmental international organisation, with 164 national standards bodies as its members. ISO develops voluntary, consensus-based market relevant International Standards that support innovation and provide solutions to global challenges (ISO, 2021). These International Standards cover a broad range of industries and technologies including food, agriculture, pharmaceutical, healthcare, to ensure that products and services are safe, reliable and of good quality, and to help facilitate international trade. Since 1947 when it was established, ISO has published over 23,056 International Standards.

ISO 9000:2015 describes universally applicable fundamental concepts, principles and vocabulary for QMSs (ISO, 2015a). It can be adopted by any organisation that wants to implement a QMS to consistently provide products and services conforming to their requirements.

ISO 9001:2015 provides requirements for a QMS that an organisation can use to demonstrate its ability to consistently provide products and services that meet customer needs and applicable regulatory requirements, and which enable improvement of the system through a process approach and the application of risk-based thinking (ISO, 2015b). It applies the following seven principles to establish the right quality culture:

1. Customer focus
2. Leadership
3. People engagement
4. Process approach
5. Improvement
6. Evidence-based decision-making
7. Relationship management

An integrated QMS is a set of policies, processes and procedures required for planning and execution in the core business areas of an organisation to meet customer requirements. Operating within a QMS framework allows a company to produce high-quality end product and meet customer requirements.

2.4 ICH Q10, Pharmaceutical Quality System - for Product Lifecycle Management

ICH Q10, developed in 2005 describes a QMS model specifically for the pharmaceutical sector; it is referred to as the Pharmaceutical Quality System (PQS). It is based on the ISO QMS and its seven principles as described in section 2.3. The right quality culture foundation is essential for the PQS, as expected in a QMS framework. Chapter One, section 1.2.3 of this thesis provides the context of why a PQS foundation, as described in ICH Q10, is an important basis for this research. It also describes why the need for a PQS was recognised in 2005 (ICH, 2005b), the key objectives, and principles of the ICH Q10 PQS framework, and why the model could be useful to implement throughout the product lifecycle in order to enhance quality and availability of medicines.

ICH Q10 establishes QRM and KM as enablers for science and risk-based decision-making in relation to product quality, and accomplishment of the PQS objectives of achieving product realisation, establishing and maintaining a state of control, and facilitating continual improvement.

Compliance with cGMPs remains a baseline expectation. In line with ISO quality and QMS concepts, ICH Q10 clearly states expectations for continual improvement and innovation. As a result of this and other ICH quality guidelines, continual improvement expectations have made their way into the cGMPs such as Chapter 1 of the European Union (EU) GMP Guide which states that:

> "*continual improvement is facilitated through implementation of quality improvements appropriate to the current level of process and product understanding*." (EudraLex, 2012)

It also requires periodic management review to identify continual improvement opportunities for products, processes and the overall PQS.

The Final ICH Q10 Business Plan, approved in November 2005 envisioned the following potential benefits for a PQS:

- *"Improved process performance*
- *A reduction in the costs of internal failures (rejects, reworks, reprocessing and investigations) as the quality systems guideline drives improvement*
- *A reduction in the costs of holding duplicate stock and operating multiple processes as improvements and changes are made more effectively across all regions*
- *A reduction in the costs of preparing / reviewing certain regulatory submissions*
- *Enhanced assurance of consistent availability of medicines to the patient."*

If only a small percentage of these costs could be avoided, then substantial saving of resources by industry and regulators will be realised and the benefits of this project will greatly exceed the costs." (ICH, 2005a)

15+ years since these envisioned benefits were laid out in the ICH Q10 Business Plan, there is abundant evidence (e.g., regarding sub-optimal process performance, failures and their costs, inventory costs, operating multiple versions of a process, drug shortages, effort and cost for preparing and reviewing regulatory submissions etc.), that the pharmaceutical sector (industry and regulators) are yet to realise these benefits. This research study instigated an inquiry for the researcher as to why, in spite of having a PQS model in place, have none of these benefits been achieved?

As the researcher took a deeper look into the ISO quality concepts that form the basis of ICH Q10, the evolution of a QMS from end product testing to early detection and prevention, and further to designing in quality into products, it led her to examine the two specific ICH Q10 objectives - *maintaining a state of control* and *facilitating continual improvement*, and whether or not these objectives might be perceived as contradictory was explored, specifically:

how to maintain control while continually improving?

The research dissected the different elements of the PQS and explored how both reactive triggers and proactive signals throughout the lifecycle of a product could (and should) be managed within the PQS, and solutions to manage these were developed. The specifics of the solutions developed are covered in Chapter Eight of this thesis. The researcher and O'Donnell published their insights in a peer-reviewed paper in the Journal of Validation Technology, titled *"Continual Improvement While Maintaining A State of Control: A Concealed Paradox or a Mutual Interdependence"* (Ramnarine *et*

al., 2019). That paper concluded that the two objectives of *maintaining a state of control* and *facilitating continual improvement* may seem to present an inherent paradox, but are in fact mutually interdependent, since a state of control cannot be maintained without continual improvement and implementation of new knowledge gained throughout the lifecycle of a product. It also concluded that the PQS, as laid out in ICH Q10, provides a holistic model to accomplish both of those objectives effectively in a systematic, transparent and structured manner.

In regards to regulatory approaches, ICH Q10 clearly states:

> "*Regulatory approaches for a specific product or manufacturing facility should be commensurate with the* ***level of product and process understanding****, the* ***results of quality risk management****, and the* ***effectiveness of the pharmaceutical quality system****. When implemented, the effectiveness of the pharmaceutical quality system can normally be evaluated during a regulatory inspection at the manufacturing site*." (ICH, 2008)

This explicitly implies that regulatory approaches may vary and the effectiveness of the PQS, including QRM application can be assessed during inspections. This eventually became the guiding vision for the recently published PIC/S Recommendation Paper on *How to Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management* (PIC/S, 2021). The researcher played a key role in the development of this guiding document which is described further in Chapter Eight, section 8.4 of this thesis. A related area of particular relevance and application to this research includes evaluating the impact of proposed changes by pharmaceutical companies and regulators, and determining what is important to communicate between regulatory assessors and inspectors in order to facilitate and ensure better management and control of risks to product quality and patient safety in the context of PACs.

ICH Q10, in its Annex 1 identifies, *Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches*; it opens the possibility of using enhanced science and risk-based regulatory approaches based on the level of product and process understanding, application of QRM, and effectiveness of the PQS. The opportunities include optimisation of PAC processes through science and risk-based approaches to:

> "*maximise benefits from innovation and continual improvement.*" (ICH, 2008)

Though ICH Q10 has been in place since 2008, these potential opportunities for advancing continual improvement and innovation have not been realised to any meaningful extent by the pharmaceutical sector.

The researcher hypothesises that this is because there has been no guidance available on what is meant by the following:

1. an enhanced science and risk-based approach
2. an effective PQS and
3. how to demonstrate effectiveness of both in order to gain regulatory flexibility and allow more PACs to be managed in the PQS without prior regulatory approval

This is the core premise of the study, the expected outcome being a transformational shift in the ability of the pharmaceutical sector to reap the benefits laid out in ICH Q10 i.e., assure availability of safe, effective, high-quality medicines in a timely manner with reduced burden for both pharmaceutical companies and regulatory authorities. The context and framework needed to achieve this are already provided through ICH Q9 and Q10. The recently published (July 2021) PIC/S Recommendation Paper has been a first significant step in providing practical guidance on how to demonstrate effectiveness specifically for the change management system (PIC/S, 2021). Similar practical implementation guidance on the other elements of the PQS namely, Management Review, CAPA, and PPPQMS is also needed.

ICH Q10 does not address the concept of mutual reliance, where regulatory authorities can benefit from leveraging each other's assessments. Through this research and its resulting solutions, it is anticipated that regulators could potentially move one step further in their journey towards harmonisation, convergence and ultimately mutual reliance, especially in relation to review and approval of PAC submissions.

2.4.1 QRM and KM – The PQS Enablers are Integral for Transforming PAC Management

ICH Q10, *Pharmaceutical Quality System*, describes QRM and KM as enablers in achieving the objectives of a PQS, and "*providing the means for science and risk based decisions related to product quality*" (ICH, 2008). ICH Q9, *Quality Risk Management*

published in November 2005, provided a structured framework, process, principles and tools for application of QRM throughout the lifecycle of a product – starting from product development, through technology transfer, commercial manufacturing and product discontinuation (ICH, 2005c). Since the publication of ICH Q9, QRM expectations have been increasingly integrated across the GMPs in many countries, and the application of QRM is an expectation across many regulatory authorities. However, no parallel guidance providing a structured framework for KM currently exists, and there is sufficient evidence that KM implementation and maturity have been lagging more so than QRM in the pharmaceutical sector, as also noted by Kane and Lipa in their respective doctoral theses (Kane, 2018; Lipa, 2021).

QRM and KM are both necessary for facilitating practical science-based decision-making, with the PQS providing clear documentation and transparency to such risk and science-based decisions. They are also intended to improve the effectiveness and consistency of product quality and patient safety related risk-based decisions, by both industry and regulatory authorities across the entire lifecycle of a product. However, in spite of the clear PQS (in ICH Q10) and QRM (in ICH Q9) frameworks, and significant efforts to implement QRM, both pharmaceutical companies and regulatory authorities have yet to realise the full potential and value of science and risk-based decision making, stated in ICH Q9 as:

> "*effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties*." (ICH, 2005c)

This was most recently referred to by ICH, when, in its published concept paper of November 2020 which described a planned 2020-2022 revision of its ICH Q9 *Quality Risk Management* guideline, it stated that:

> *"the benefits of QRM, as envisaged by ICH Q9, have not yet been fully realized.*"

and it indicated that product availability risks and risk-based decision-making, two areas of direct relevance to this research work, were areas in need of improvement (ICH, 2020).

So why is this the case? The researcher hypothesises that even though ICH Q9 and Q10 collectively discuss that QRM and KM can improve risk-based decisions, there has been insufficient attention or clarity on what good risk-based decision-making looks like and how it might be achieved. This is also supported by the aforementioned ICH Q9(R1) 2020 Concept Paper.

Utilisation of these enablers should begin early in development and continue all through the product lifecycle, incorporating new knowledge that continues to grow through the commercial life of the product to drive risk reduction and continuous improvement. This is essentially the basis for ongoing product lifecycle management, including PAC management – hence its relevance to this research.

Lipa's research explored the integration of QRM and KM and resulted in a very useful risk knowledge infinity cycle (RKI) (Lipa, O'Donnell and Greene, 2020). This cycle shown in Figure 2.7 below is a continuous cycle where knowledge flows to inform risk and an understanding of risk informs new knowledge. Lipa et. al. further published case studies demonstrating how to utilise the RKI cycle for specific instances across the product lifecycle (Lipa *et al.*, 2021). Application of the RKI cycle for PAC management to drive continual improvement and innovation as another application area is further described in Chapter Nine, section 9.1.4 of this thesis.

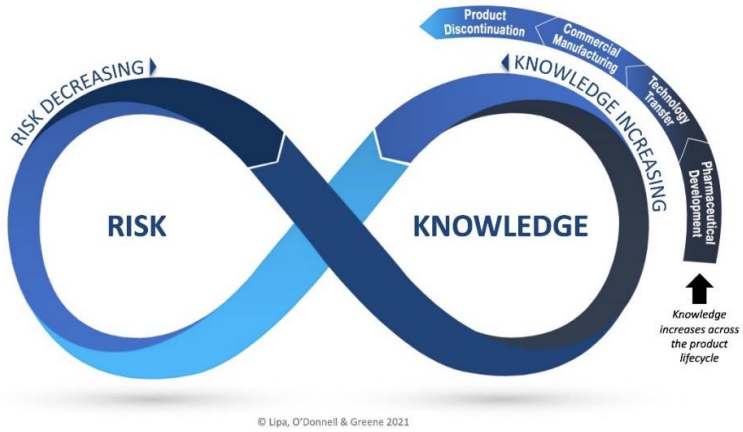

Figure 2.7: The RKI Cycle Applies Throughout the Product Lifecycle (Lipa, O'Donnell and Greene, 2020)

The risk - knowledge relationship as demonstrated by Lipa's work, can be applied to any QRM activity across the product lifecycle. This holds true even for PAC management. The better the knowledge and understanding base from the pharmaceutical development phase of a product's lifecycle, the more effective it is to continue to build the experience space from this base, as the product progresses into its commercial life. A strong product development knowledge base also improves the level of rigor and quality of the risk assessments that are needed to manage the product and its control strategy, including PACs, throughout the product lifecycle. Higher product and process understanding are expected to drive risk reduction, which in turn can activate flexible regulatory approaches. Such flexible regulatory approaches can facilitate risk-based regulatory decisions for reviews and inspections, enable process improvements with reduced regulatory oversight, and reduce the number of post-approval submissions that may be required. Enhanced product and process understanding is essential to gain this regulatory flexibility.

Connecting back to the ISO quality concepts and evidence-based decision-making, one of the seven principles, evidence-based decision making, a science and risk bases becomes fundamental to:

1. evidence-based decision-making related to product quality and patient safety
2. an effective PQS
3. the right quality culture and mindset

ICH Q9 refers to, but was deemed to not adequately address QRM application for the management of product availability (i.e., drug shortage) risks. There was evidence through the continuing global drug shortages problem that such risks, when not well managed, ultimately impact patients. The strategic importance of an increased emphasis on managing product availability risks, through risk-based drug shortage prevention and response plans, can be linked directly to protection of public health by serving the interests of patients well.

In July 2017, Dr Kevin O'Donnell initiated the development of a proposal to revise ICH Q9 to address the topic of risk-based decision making and QRM application for product availability risks (along with two other points, not directly related to this research). The proposal recognised that when ICH Q9 was published in November 2005, ICH Q10 had

not yet been in place, therefore the concepts of QRM and KM as being enablers of the PQS and as means to drive continual improvement and innovation, had not been fully articulated. The final ICH Q9 revision proposal was endorsed by ICH in October 2020 with Dr O Donnell appointed as the Rapporteur (ICH, 2020).

2.4.2 Demonstrating Pharmaceutical Quality System Effectiveness and Driving Continual Improvement: Evidence-based Risk Reduction

The research explored how risk-based decision-making might be improved in the pharmaceutical industry in order to understand what the barriers to innovation are, and how they may be overcome. Through 15 years of active and practical experience with implementing QRM in the industry, the researcher learnt that risk-based decision-making was indeed weak, and that the link between the initial steps in the QRM process i.e., planning and performing the risk assessment using various methods and tools, and the subsequent decision-making steps, was either broken or often subjective and passive. Therefore, the QRM and the PQS frameworks as envisioned in ICH Q9 and ICH Q10 were still far from full implementation and realisation.

The researcher, together with O'Donnell, explored this area and it was part of the preliminary body of work leading up to this study. The resulting peer-reviewed publication *"Demonstrating Pharmaceutical Quality System Effectiveness and Driving Continual Improvement: Evidence-based Risk Reduction*" described that there is not a well-established link between product and process knowledge (which is dynamic and continues to evolve during the lifecycle of a product) and control strategies, such that it can lead to continual improvement and innovation (Ramnarine and O'Donnell, 2018). The paper presented how **evidence-based risk reduction** could be the mechanism to establish this link in utilising the latest product and process knowledge to not only ensure that the control strategy is robust and effective, but to also drive continual improvement and innovation. The basis for evidence based-risk reduction are data that are related to the effectiveness of risk-based mitigating controls; such data can also be derived from assessments of the robustness of controls when testing at the edges of failure, and when performing worst-case validation studies etc. Controls that did not lend well towards data-based assessments of their effectiveness e.g., procedural or

training controls, tended to be more difficult to generate risk-reduction evidence for. The authors concluded that the only way to achieve regulatory relief and flexibility (as envisioned in ICH Q10 and eventually carried into ICH Q12) in PAC management was to utilise enhanced science and risk-based approaches and make this transparent within the construct of an effective PQS that is capable of assuring a state of control and enabling continual improvement.

Building on the importance of evidence basis described in that paper, the researcher asserts that when data-based evidence is provided to show that a PAC (which results in process improvement, continual improvement or innovation) could reduce current risks to product quality and/or patient safety, this should serve to build trust with regulators and facilitate confidence among regulators such that regulatory flexibility can be provided to companies for faster implementation of such PACs. It would form the basis for companies demonstrating to regulators that their risk-based decision-making processes were sound, based on objective evidence, and backed by science and data. Additionally, it could also be a mechanism to determine where companies and regulators should focus their resources. Could all of this be achieved through qualitative or subjective assessments, was a question posed. Possibly, but not in a rigorous manner that engendered confidence and trust in the risk-based decision-making process and the resulting decisions. Without this, it would not be possible to realise the vision of ICH Q9, Q10 and Q12.

Other industries, such as aerospace and nuclear power generation, have been well-ahead of the pharmaceutical industry with regard to established risk-based decision-making processes; while it is not the subject of this research, the paper proposed that there was merit for the pharmaceutical industry in leveraging the learnings from these other industries. It also proposed specific areas to look into to improve evidence-based risk reduction and decision-making in the pharmaceutical industry.

2.5 ICH Q12, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

In September 2014, the ICH Steering Committee endorsed a Concept Paper for a guideline that:

> *"will provide a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle. Adoption of this guideline will promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments. It will allow regulators (assessors and inspectors) to better understand, and have more confidence and trust in a firm's Pharmaceutical Quality System (PQS) for management of post-approval CMC change."* (ICH, 2014)

This ICH Q12 Concept Paper acknowledged that absence of harmonised approaches for technical and regulatory aspects for product lifecycle management impeded innovation and continual improvement in the pharmaceutical industry. It recognised that though ICH Q8 through ICH Q11 focused well on product development stages, there wasn't adequate guidance on utilisation of science and risk-based assessments for product lifecycle management throughout the commercial life of a product. Further, though ICH Q10 laid out the framework for all elements of the PQS, the ICH Q12 Concept Paper emphasized the need to develop further details on the change management system such that it enabled transparent, harmonised understanding with regulators (inspectors and assessors) and their confidence and trust in a company's capabilities to effectively utilise the latest product and process knowledge to implement changes, and justify the desired operational and regulatory flexibility that was being sought by companies. Implementation of harmonised change management could facilitate more transparency and efficiency for both regulators and pharmaceutical companies, thereby improving supply reliability and product availability. It further anticipated one of the benefits being mitigation of drug shortages related to manufacturing and quality problems through strategic management and use of science and risk-based approaches for PACs.

The vision, expectations and resulting benefits identified by the ICH Q12 Concept Paper, aligned completely with the researcher's work including the PAC iAM^{SM} Task Force's charter she was co-leading at the time. A component of the researcher's work

and the Task Force's charter was to provide active input including draft content to the ICH Q12 Expert Working Group (EWG) and contribute towards the development of the ICH Q12 guideline. This also included providing practical recommendations and real-world examples from the pharmaceutical industry to facilitate development and implementation of ICH Q12.

In order to achieve this, the researcher in her capacity as co-lead of the PAC iAM^{SM} Task Force, influenced and contributed to ICH Q12, by developing and proposing draft text to the ICH Q12 Expert Working Group (EWG) for:

- product lifecycle management including a template for a product lifecycle management (PLCM) plan
- vision of an effective PQS for PACs
- change management considerations for PACs

Published in November 2019, ICH Q12 is the latest finalised ICH quality guideline; it provides a framework for managing PACs more efficiently and predictably, such that continual improvement and innovation, as expected by ICH Q10, can be promoted (ICH, 2019). ICH Q12 expands on the flexible regulatory approaches for post-approval CMC changes that have been referred to in ICH Q10 Annex 1. It brings alignment on terminologies such as established conditions, product lifecycle management; provides a series of regulatory tools and enablers; and it describes how these can be used to integrate the latest product and process knowledge, understanding of risks, and the framework of an effective PQS to determine the appropriate regulatory reporting categorisation for a PAC, and to allow more PACs to be managed within the company's PQS with reduced regulatory oversight. The concepts and tools provided in ICH Q12 have a strong underlying construct of risk and knowledge basis, and include the following:

- A risk-based decision tree for categorisation of PACs
- Established Conditions (ECs)
- Post-approval change management protocol (PACMP)
- Product lifecycle management (PLCM) document
- PQS and change management

- Structured approach for frequent PACs without the need for prior regulatory approval
- Stability data approaches to support the evaluation of CMC changes

The ICH Q12 guidance has been in place for under two years, so it remains to be seen what its level of adoption and value delivery will be in terms of accelerating continual improvement and innovation through faster PAC management.

This research expanded specifically on how to apply the ICH Q12 concepts and tools for the risk-based categorisation of PACs, PQS and change management. It delved into how increased collaboration between regulatory assessors and inspectors was essential for the successful implementation of ICH Q12.

For categorisation of PACs, the ICH Q12 guideline described a risk-based approach that utilised current product and process knowledge to determine the level of risk associated with a change. Moderate to low-risk changes could be managed via a regulatory notification and did not require prior-approval by regulatory authorities. Changes that did not require regulatory reporting via prior-approval or notification could be documented and managed only within the PQS, and verified by inspectors during routine inspections. This was a useful step in the direction of regulatory flexibility – it set out a path for easing the regulatory burden for those companies which merit it, whilst still affording oversight by regulators. However, it should be noted that, for countries which do not have notification pathways within their regulatory framework, the current state of requiring prior-approval would likely continue.

The guideline defined Established Conditions (ECs) as:

> "*legally binding information considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority*." (ICH, 2019)

It described how to identify ECs based on product and process understanding. A decision-tree with a step-wise approach to identify ECs and reporting categories for changes to them were provided. A change to an EC requires reporting to regulatory authorities (either as a prior-approval submission or a notification, depending on the risk level). For changes to non-ECs, no reporting is required, and such changes may be managed solely within the company's PQS.

An effective PQS per ICH Q10 was considered necessary for use of the ICH Q12 tools. The guideline illustrated the connection between change management and knowledge management, and how this could be linked to the regulatory process for the management and reporting of changes to ECs. Appendix 2 in ICH Q12 provided twelve change management principles for effective PAC management, including - proper change planning, utilisation of existing product and process knowledge, application of science-based risk management for assessment of risks associated with a change and identification of appropriate risk controls, determination of data required to implement the change, ensuring appropriate regulatory submission, adequate implementation planning for the change, verification of effectiveness post-implementation, and documentation of new knowledge post-implementation.

The guideline highlighted the importance of collaboration and effective communication between regulatory assessors, who reviewed the PAC filings, and inspectors who inspect the effectiveness of the PQS at manufacturing sites. PQS gaps found by inspectors could be used by assessors in their review and decision-making for PACs. Similarly, inspectors being aware of the latest product lifecycle management information from a filing, could be useful during inspections, in order to assess whether the company's PQS is adequate, capable and effective in managing a product through its commercial life in the context of PACs.

Finally, the ICH Q12 annexes provide examples of identifying ECs for manufacturing processes and analytical procedures, PACMPs and a PLCM document.

ICH Q12 training is still under development. Implementation of ICH Q12 first requires the implementation of ICH Q8(R2), Q9, Q10 and Q11. Therefore, these ICH quality guidelines have built upon each other and are interconnected, in that companies cannot realise the value of ICH Q12 unless the preceding guidelines have been well-implemented.

ICH Q12 does not specify how a company's risk-based decision-making process, utilising the latest product and process knowledge, could be integrated into its change management system, or how the decision-making by a company utilising these concepts from a PQS perspective could be integrated with decision-making by regulators from a

regulatory CMC perspective. This research, therefore, explored opportunities on both of these aspects such that mutually integrative decision-making by pharmaceutical companies and regulators in relation to PAC management could result in the desired state of faster and more timely continual improvement and innovation.

2.6 Literature Published by the Researcher Prior to Initiating the Research Study

The researcher's experience with QRM, PQS, drug shortage management, and PAC management, spanned over 16+ years; details of this experience and related literature are depicted above in Figures 2.2 and 2.3, and described in Appendix I, but are not included in this chapter. Key publications from that body of work that directly relate to this research such as PDA Technical Report 68, are described in this thesis while others are provided as supporting evidence for this research. These draw the link between the researcher's journey towards this research study, starting with her initial body of work in QRM, its evolution into the specific application of QRM in addressing the problem of drug shortages, and from there towards product lifecycle management and PAC management, the topic of this research.

2.7 Literature Review Summary

The literature review provided in this chapter was built both on broader reviews conducted through several PRST doctoral dissertations on QRM, KM and PQS, and on a targeted review specifically for drug shortages; it explored published data and insights, linking limited continual improvement and innovation to drug shortages. With regard to the latter point, very little has been published to date, and not unexpectedly so, because of the high complexity and challenge associated with drawing such a correlation. The literature review further confirmed how little progress has been possible, not only because of the complexity of this 'wicked problem', in spite of good intent and significant effort, but also that QRM, KM and PQS maturity are a long way from the state desired (when compared with other mature industries such as nuclear or aerospace) that is necessary to achieve the objectives and value proposition laid out by this research study. It also reaffirms the importance of tackling this problem, whilst acknowledging that this will be a long journey.

The next chapter presents the research design, methodology and methods utilised for this study and the researcher's perspective based on her prior work and practical application experience.

Chapter Three

Research Design, Methodology, and Methods

This chapter describes the research design, methodologies and methods utilised for this research study. As mentioned in Chapter One and Chapter Two, and described in Appendix I of this thesis, the pre-research body of work conducted by the researcher, coupled with her direct pharmaceutical industry experience with managing PACs, building Quality Systems and being a QRM expert, lent a pragmatic insider's perspective to the work. It also permitted a real-life, bona fide and attestable worldview to be applied to the research. This chapter also outlines the methodology and methods used for the specific research questions, as well as the research ethics, confidentiality and privacy considerations.

3.1 The Researcher's Worldview

The researcher's direct experience in the pharmaceutical industry coupled with her 6+ year prior pre-research work that eventually led to this research study, served to formulate the researcher's philosophical worldview assumptions in the context of this research. Creswell and Creswell introduced the term 'worldview' (Creswell and Creswell, 2020) in lieu of 'paradigm' defined by Guba as "*a basic set of beliefs that guide action*" (Guba, 1990). These worldviews or paradigms also guide disciplined inquiry by a researcher (also known as research methodology).

In developing the research problem and research hypothesis, the researcher needed to probe her own beliefs and philosophical assumptions. The researcher's broader philosophical belief and sense of purpose is one rooted in the bottom-line importance of serving the needs of, and bringing value to, others through everyday actions. Specifically, within the pharmaceutical sector, this philosophical belief has directly translated into actions that serve the needs of patients and public health, current and future.

Extensive literature has been published on various inquiry paradigms with three specific ones of particular relevance noted by Guba (Guba, 1990):

1. *Ontological: What is the nature of the "knowable"? Or what is the nature of "reality"?*
2. *Epistemological: What is the nature of the relationship between the knower (the inquirer) and the known (or knowable)?*
3. *Methodological: How should the inquirer go about finding knowledge?*

For the purpose of this research, and guided by her philosophical beliefs and personal experiences, the researcher based her *ontological* reality on works and practical actions that result in benefiting and serving patients' needs and improving public health. From an epistemological perspective, the researcher holds the belief that the current state of public health is not being served well, as objectively and subjectively evidenced by the ongoing issue of drug shortages and the slow pace of continual improvement and innovation during lifecycle management of commercial pharmaceutical products. If continual improvement could be accelerated, it would not only reduce drug shortages, but advance innovation that could reduce risks to patients (e.g., improved control systems).

Creswell highlighted four worldviews that have been discussed widely in published literature; these are shown in Table 3.1 below (Creswell and Creswell, 2020):

Table 3.1: Four Worldviews (Creswell and Creswell, 2020)

Postpositivism	**Constructivism**
• Determination • Reductionism • Empirical observation and measurement • Theory verification	• Understanding • Multiple participant meetings • Social and historical construction • Theory generation
Transformative	**Pragmatism**
• Political • Power- and justice-oriented • Collaborative • Change-oriented	• Consequences of action • Problem-centered • Pluralistic • Real-world practice oriented

3.2 Worldview Basis for Research Inquiries – Pragmatism, Transformative and Systems Thinking

During the initial course of this research and through the exploration of the 'wicked problem', two worldviews were found to be primarily applicable – *pragmatism* and *transformative,* with *constructivism* having a secondary relevance in relation to viewing the complexity of a 'wicked problem' from the perspective of the different stakeholder groups. These are expanded upon below:

- *Pragmatism*: For Phases 1 (Problem Definition), 2 (Exploring the 'Wicked Problem' and Regulatory Authorities' Positions) and 3 (Bringing the Pharmaceutical Industry Together – to establish the *1VQ for PAC Initiative*) of the research study, the researcher most associated with the worldview of *pragmatism* with a secondary component of *constructivism*.

  Given the high complexity of a 'wicked problem', the researcher needed to be open to highly divergent and sometimes conflicting viewpoints. This was entirely expected for a 'wicked problem', as described in Chapter Four, section 4.2 of this thesis, namely that *every problem is unique and difficult to clearly define*, whereby not all stakeholders' views fully aligned on the problem or its solutions. The *pragmatism* worldview afforded the researcher the flexibility of utilising mixed methods to investigate the 'what' and the 'how' for the problem, based on the intended consequences. This research study necessitated the use of mixed methods, whereby multiple methods, specific aspects from different worldviews, including a range of related assumptions, and a mix of qualitative and quantitative data could be considered to seek a reality-based understanding of the research problem and sharpen the research questions.

  Instead of looking at the problem from the narrow view of any single stakeholder group, the research study intended to explore the views of two of them – the pharmaceutical industry and regulatory authorities. A commonality for these two stakeholder groups is that their work and decisions are supposed to be science and data-based. Therefore, if they align on a standard science-based global approach, it could transform PAC management and reduce drug shortages.

The study did not delve into the detailed views of healthcare providers, policy makers, governments or legislators, but acknowledged that each stakeholder's perception of the 'wicked problem', and therefore its solutions, may not be the same, given that their relative realities may vary. (This is where a *constructivisim* worldview would become important, especially if one were to expand the exploration of this problem to the interfaces, touchpoints, interconnectedness or interdependencies across all these communities. This, however, was not within the scope of this research, hence the secondary relevance of a *constructivism* worldview.)

- *Transformative*: For Phases 4 (Exploring and Developing Practical Science and Risk-Based Solutions) and 5 (Application to Specific PAC Example Case Studies) of this research study, the transformative worldview was most relevant, as envisioned by the overarching goal of this research:

  > *to accelerate continual improvement and innovation, and reduce global complexity* ***through science and risk-based transformation*** *of PAC management – so that the pharmaceutical sector can ensure uninterrupted delivery of safe, effective, high-quality medicines to patients.*

  The 'wicked' nature of this problem, with its characteristic high level of complexity, multi-causal, multi-factorial, multi-stakeholder interfaces, and interconnectedness, where every problem is a symptom of another problem, meant that an incremental approach to finding its solutions would not suffice. A transformative worldview whereby *systems thinking* as described further below must be applied, emerged as being necessary to address the problem. The transformative nature of this research enabled the researcher to:

  a) raise consciousness and awareness of the global problem
  b) articulate impact to patients
  c) provide a voice for contributing participants at a senior leadership level where decisions are made
  d) establish a unified voice for reform, change and transform PAC management for the ultimate benefit of patients

e) work collaboratively across different stakeholders and geographies in the pharmaceutical sector to iteratively define the problem and the development of the resulting standard solutions, and
f) think differently than what had been done for almost decades with limited to no results (in terms of overcoming the global regulatory complexity for PAC management)

- *Systems Thinking*: During the course of the research, particularly when developing the standard solutions in Phase 4 (Exploring and Developing Practical Science and Risk-Based Solutions), evaluating approaches for piloting and implementing those solutions, and for Phase 6 (Impacts and Future Opportunities), an unexpected new worldview emerged for the researcher, that of '*systems thinking'*. Even though this research did not deeply explore the sociological, geopolitical, behavioural or cultural contexts of the research problem, *a combination of the transformative, pragmatist and systems thinking worldviews* provided the optimal space for this research to acknowledge the relevance and importance of these contexts in addressing the 'wicked problem'.

Given the value and significance of the *systems thinking* that emerged for the research questions investigated in this study, the next section expands on what *systems thinking* is, why it was important for this research topic, and how it was applied during this work.

3.2.1 Systems Thinking Worldview

Systems thinking is simply:

> *the ability or skill to perform problem solving in complex systems* (Wikepedia, 2021).

A system is:

> *"a group of interacting interdependent parts that form a complex whole."*(Montuori, 2011)

In other words, a system is an entity with interrelated and interdependent parts; it is more than the sum of its parts (subsystems) - it is an ecosystem, where every subsystem

depends on every other subsystem, either directly or indirectly; therefore, an awareness and understanding of the boundaries of those parts is of fundamental importance.

The concept of *systems thinking* goes back to the ancient Mayan and Egyptian times; the term 'general systems theory' was coined in the 1940 by Ludwig von Bertalanffy who developed a new approach to study living systems (Von Bertalanffy, Braziller and York, 1968). It encompasses an approach to inquiry that is not limited to one discipline, and proposes a new way of thinking about the world, focusing on interconnected, interdependent, dynamic systems, rather than parts that can be isolated from the whole (Montuori, 2011).

Systems inquiry, as a worldview, was initially not part of the researcher's study design, but with the exploration of the characteristics of a 'wicked problem', and while designing standard solutions for operational implementation by pharmaceutical companies and their acceptance by regulators, *systems inquiry* and *systems thinking* emerged as an important basis to examine the problem. This was so that the design of solutions could address multiple subparts of the system as connected and part of a whole, as opposed to isolated, independent, self-contained entities. It became increasingly clear that changing one part of the system affected other parts of the whole system. So, although not consciously planned within the study design, *systems thinking* was applied in designing the standard solutions, where instead of identifying what other stakeholders needed to change, the exploration of the problem and the design of the solutions considered what would work across stakeholder groups. An example of this is transparency for both pharmaceutical companies and regulatory authorities on how decisions are made for PACs.

Beyond this, the considerations also needed to further extend to the individuals working as a part of the system, as they are components of the system too, and therefore, they contribute to its outcomes. *Systems thinking* is intended to drive user-centred processes and solutions, in this case, the end user being the patients who expect and deserve their medicines to be on time, every time.

While the scope of this research was primarily limited to the pharmaceutical sector, the researcher acknowledges that these are only two subsystems within the whole which

involves many other organisations and stakeholders, as described in Chapter One, section 1.2.3 of this thesis. However, if these two subsystems could collaborate and agree on solutions, it would result in a meaningful impact in advancing innovation and continual improvement in the pharmaceutical industry, and reducing drug shortages.

The general modus operandi in the pharmaceutical sector has remained that, regulatory authorities establish expectations and requirements primarily at a national or regional level, as *guidance for industry* that then must be implemented by those companies. Calnan in her thesis reviewed and researched how decades of emphasising compliance as a means to achieve quality might have limited continual improvement and innovation in the pharmaceutical industry and beyond complying with the cGMPs, the pharmaceutical sector (both industry and regulatory authorities) must adopt mainstream quality management standards and principles (Calnan, 2014). This was indeed the intent of the ICH Q10 PQS model, but thus far, the ISO 9001 quality management-based concepts that ICH Q10 has been based on, have not been realised; this has been a divergence for the pharmaceutical industry from other ISO managed non-pharma industries that have also implemented QMSs.

Many regulatory authorities have a practice of inviting feedback on draft regulatory guidances before they are finalised and brought into force. Beyond this practice, over the last few years, some regulatory authorities and organisations such as FDA, PIC/S and WHO, have started inviting more collaboration with the industry through pilot projects. These have related to the implementation of tools and concepts, such as PQS maturity assessments, inspection protocols, established conditions, etc.

An interesting insight the researcher gained during the course of the study was that, there have been very limited, if any, collaborative proposals made by the pharmaceutical industry to regulatory authorities or vice-versa, and there is also no *guidance for regulators* that can facilitate harmonisation across assessors on PAC assessment and decision-making. A *systems worldview* propounds that, involved individuals or stakeholder groups must constantly be aware of and understand the boundaries between their respective subsystems, and design solutions that are not linear in addressing only their individual parts, but the whole. It is contrary to the conventional

tendency to reinforce organisational boundaries through structures, systems, policies, etc.

John Atkinson, a systems thinker and thought leader, states that:

> *"messy complex problems are just too hard for individuals to comprehend, so we parcel it up into packets of problem we can understand and manage and tell ourselves that we have done a good and right thing."* (Atkinson, 2018)

Systems thinking challenges the notion and assumption that, the way we run an organisation – be it a regulatory authority, pharmaceutical company, government, legislative or policy-making body, hospital, distribution channel, or country - is how it should be run to serve its purpose and be of value to society, that each stakeholder must design and own their solutions within their respective organisational accountabilities, and that our control or even influence is limited beyond our own organisation's primary and maybe, secondary boundaries that interface with another organisation. This research study design intended to first facilitate the pharmaceutical industry looking inwards to determine what they could do to contribute towards solving the problem, and then collaborate with regulatory authorities to enable joint application of the resulting solutions.

Organisations certainly manage relationships with other organisations they need to interface with, but this is typically linear and within their positional power and hierarchies; however, in a *systems world*, power is dispersed, the relevance of traditional positional authorities must be diminished and set aside in order to connect, collaborate and jointly solve issues for the collective good of the society. Current organisational setups, systems and ways of working tend to inherently push back on complex challenges and usually try to band-aid fix them, which usually adds more complexity or bureaucracy. The global complexity with respect to increasing local and regional requirements is an example of this, and yet drug shortages continue.

Therefore, several system scientists such as Atkinson and Myron Rogers have asserted that 'wicked problems' are addressed by asking questions and not following standard operating procedures. The questions include:

- *"Who are the 'we' who have a collective interest and energy for addressing the problem we face?*

- *What do we individually and collectively know about what is going on in order that we might make more sense of what we are trying to do?*
- *How well do we connect to each other so that we might have the opportunity to decide where to place our efforts?"* (Atkinson, 2018)

To address these questions, it is critical to have the same level of awareness and a common understanding of a problem and its implications, before it can be solved. The ability to work with multiple perspectives, value insights and knowledge offered by each of those perspectives, but not at the exclusion of others, and to harness the collective power of the sub-parts of a whole living system to co-create solutions is the fundamental basis of *systems leadership* (Atkinson, 2018). As new connections form between stakeholders, new patterns, relationship formats and interaction pathways emerge, and transformative solutions that once could not be conceived, become possible. At the same time this might challenge existing ways of finding coherence, and even lead to the collapse of conventional or traditional ways of working.

With these new insights related to *systems thinking*, even though it might seem atypical (relative to conventional ways of working in the pharmaceutical sector), the researcher decided to develop use case studies for the developed solutions while the research study was still ongoing. It was considered imperative, given the iterative nature of this research and the multiple perspectives involved, that the solutions be developed through active collaborative dialogue and input-gathering, from both pharmaceutical companies and regulators, even as the research study was in progress. Exchange between regulators and pharmaceutical companies for the development and implementation of these standard solutions formed an integral component of the *systems approach* used in this research study. The researcher posits that this exchange was paramount, not only for calibration and alignment between the pharmaceutical industry and its regulators on a common understanding of the problem, but also in the interpretation and acceptability of the solutions. Therefore, this research aimed to facilitate such exchange between the pharmaceutical industry and regulatory authorities. The exchange also served a valuable means for pharmaceutical companies to build credibility and trust with regulators.

A *systems thinking* approach to working across organisational boundaries to address the issues of mutual concern (i.e., slow continual improvement and innovation contributing to drug shortages), was imperative. It was considered key for testing and gaining

adoption of the solutions within the pharmaceutical industry, and their acceptance by regulators. To wait for completion of this PhD, before the solutions were made available for testing and adoption, would have been a missed opportunity in advancing this topic with a sense of urgency. TU Dublin, through this research, intends to make an invaluable academic contribution to a current, real and growing global problem for the pharmaceutical industry, its regulators, and ultimately the patients who rely on medicines.

With this framing of the researcher's *pragmatic, transformative and systems* worldview for this study, the next section elaborates on the insider's perspective that the researcher brough to this body of work.

3.3 The Researcher's Insider Perspective

As stated in Chapter One and Chapter Two of this thesis, the researcher had been employed in the pharmaceutical industry for 20+ years and, prior to registering for this research, undertook activities as part of her pharmaceutical industry affiliation which served to provide an important pre-research foundation to this study. The researcher's high-level career experience informing this research and her prior registration pre-research work are provided in Appendix I of this thesis.

The researcher acquired over 15+ years of practical QMS and QRM application experience for the pharmaceutical development, technology transfer and commercial manufacturing phases of a product lifecycle, across the medical device, biopharmaceutical and pharmaceutical sectors. She also managed global validation and change management processes, in addition to establishing a QRM program with policies, procedures, tools and training for her company, and facilitated risk assessments. Outside her company, she provided QRM training sessions and held QRM application workshops for the industry and regulators. Additionally, in her position of leading a Global Analytical Science and Technology function and managing QC operations within her pharmaceutical company of employment, the researcher also acquired direct first-hand experience with operational aspects of product and process knowledge management, PAC management, regulatory submissions and the associated

quality, operational, regulatory and supply processes. All of this experience is summarised in Appendix I of this thesis.

Given the researcher's employment in a pharmaceutical company and the deep experience she gained with QRM, QMS, PAC management and product lifecycle management, the researcher acknowledges having an insider's and a practitioner's perspective when undertaking this research, thereby making some of this study insider's 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, 2002), or "*insider research is that which is conducted within a social group, organization or culture of which the researcher is also a member*." (Greene, 2014). An article by Rooney on the validity of insider research is also useful in this context (Rooney, 2005).

A researcher's insider perspective has advantages (pros) and disadvantages (cons); Greene categorised them as follows (Greene, 2014) and Lipa summarised them succinctly in his PhD thesis as given below (Lipa, 2021):

- "***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."*

Specific to this study, the advantages that the researcher's insider's perspective lent to this research included the following:

- Understanding and knowledge of the vision, expectations, along with the operationalisation experience, of QRM, PQS and PAC concepts, which expedited the researcher's ability to probe further with targeted inquiries
- Access to a broad network of Operations, Quality and Regulatory Affairs practitioners in pharmaceutical companies, and to assessors and inspectors in different regulatory authorities
- Familiarity and knowledge of risk management and QMSs within and beyond the pharmaceutical sector
- Familiarity and deep application and practical operational experience with QRM, KM, PQS, drug shortages, and PAC management
- Understanding what approaches had been tried with limited success, and seeking alternate ways to design the research queries, such as exploring it from the perspective of a 'wicked problem' and *systems thinking*

It should be noted though that, while still remaining employed in the pharmaceutical industry, when the researcher started this research study, she was no longer in a role that involved QMS, QRM or PAC management; instead, she did this research while holding a position in product CMC development (i.e., prior to product commercialisation), with no direct involvement in PAC management for commercial products. This allowed her to have a degree of separation by no longer being active or connected within the community directly responsible for PAC or PQS management within her company of employment, or with regulators on PAC submissions, or PQS inspections. Additionally, being mindful of the potential risk of bias and subjectivity, the researcher mitigated these through the following means:

- Utilising a mixed methods approach that incorporated both qualitative and quantitative data as described in section 3.5
- Gathering diverse insights and even divergent viewpoints from multiple and varied stakeholder groups, i.e., Operations, Quality, Regulatory stakeholders from the industry (those involved in direct execution as well as senior leaders), regulatory authorities' assessors and inspectors from a broad range of countries

or regions (those involved in direct execution as well as senior leaders), and academia

- Utilising a variety of channels to gather data, i.e., conferences, presentations, focus group sessions, workshops, surveys, interviews, dialogues
- Utilising an iterative approach to gather input, develop solutions, socialise for feedback (with each solution being reviewed by 250 - 400 people across the pharmaceutical sector), collect and adjudicate comments, refine the solutions before finalisation and publication as peer-reviewed papers. This approach was particularly important and useful in mitigating the risk of 'group think', limiting bias and promoting further objectivity

In spite of having an insider's perspective, the researcher approached this study from neither the pharmaceutical industry nor a regulatory authorities' viewpoint. The researcher's interest for this topic was entirely driven by her broader philosophical beliefs, purpose and commitment to serve the needs of patients and public health by creating a space for stakeholders to explore solutions together as opposed to unilaterally or independent of each other. It was this interest and passion that motivated her to take on an outsider's view and utilise the neutral and broader academic research space to pursue this topic. As such, her pre-research and research work on all aspects of this topic since 2012 have been independent of the researcher's employer. Through the course of the research, she further realised the tremendous value in exploring this complex 'wicked problem' as an academic researcher, as opposed to trying to solve it as a pharmaceutical industry professional. The researcher's employer did not influence any aspect of this research or the researcher's perspectives, research methods or the results generated herein.

3.4 A Brief History of the Research Questions

The original research proposal for this study was developed utilising the insights gained from the pre-research work undertaken by the researcher as described in Chapter Two and Appendix I of this thesis. The research proposal included in the research application and registration package submitted to TU Dublin was based on the following research hypotheses:

1. *The increasing complexity of the global regulatory framework for managing PACs is hindering the objectives of product realization, maintaining a state of control and driving continual improvement to ensure that safe, high-quality products are available to patients – it causes a significant time gap between new knowledge gained for products and processes, and its implementation into daily operations. Because of this global complexity, companies prefer to maintain status quo rather than continually improving and innovating their operations; this eventually results in drug shortages*
2. *A second hypothesis is - although regulators, industry and patients alike desire an uninterrupted supply of high-quality products, and all favour innovation and continual improvement - local solutions, or solutions designed by one stakeholder population independently, will not resolve this problem*

These hypotheses guided the researcher's literature review and her initial discussions with various stakeholders in the pharmaceutical industry, regulatory authorities and academia, specifically TU Dublin PRST members. As work per the research plan progressed, the overarching goal of the research further solidified to the following:

> ***To accelerate continual improvement and innovation, and reduce global complexity through science and risk-based transformation of PAC management – so that the pharmaceutical sector can ensure an uninterrupted delivery of safe, effective, high-quality medicines to patients.***

The research hypotheses were also further refined as follows:

1. *The high global regulatory complexity in relation to PAC management incentivises the pharmaceutical sector to maintain status quo rather than continually improve and innovate their operations and technologies*
2. *Without the effective use of QRM and KM to manage the lifecycle of products, processes and systems within the PQS, the PQS cannot be effective; and without an effective PQS, it is not possible to **"optimise science and risk-based post-approval change processes to maximise benefits from continual improvement and innovation"** in accordance with ICH Q10 Annex 1*
3. *Without continual improvement and innovation post-approval, the pharmaceutical sector cannot sustainably ensure the timely and uninterrupted delivery of safe, effective, high-quality medicines to patients*

The following concepts and associated inquiries were then derived from these hypotheses:

Concept 1: Drug shortages are a 'wicked problem' and the global complexity associated with PAC management further aggravates this problem.

Associated Queries:

- What is a 'wicked problem' and what are its characteristics?
- What characteristics make drug shortages a 'wicked problem'?
- Why are continual improvement and innovation relevant for drug shortages?
- What makes the global regulatory landscape complex?
- Why does the complexity of the global regulatory landscape matter?

Concept 2: A science, risk and knowledge bases within the framework of an effective PQS are essential for continual improvement and innovation. However, beyond the high-level concepts stated in ICH Q10 and Q9, there has been little to no practical guidance on how companies can actually demonstrate the effectiveness of a PQS or on the application of risk-based application of QRM principles for PAC management.

Associated Queries:

- What is the relevance of a QRM, KM and PQS framework for PAC management? Why are they integral for transforming PAC management?
- What could effective science and risk-based PAC management look like? How could it be achieved?
- What is meant by an effective PQS? How could it be demonstrated?
- How could a science, risk and knowledge bases and an effective PQS facilitate faster continual improvement and innovation and how could it contribute to reducing drug shortages?

A third concept that wasn't envisioned as part of the research plan but that started emerging towards the later part of this research study linked back to a fundamental question reflecting on why ICH Q10 and Q9 had had a lack of success in reducing defects and facilitating continual improvement. Even though ICH Q10 had laid out 16+ years ago a clear quality system model with the following envisioned benefits, why has

there been limited to no realisation of these benefits; in fact, for some of these, the situation has worsened?

- *"Improved process performance*
- *A reduction in the costs of internal failures (rejects, reworks, reprocessing and investigations) as the quality systems guideline drives improvement*
- *A reduction in the costs of holding duplicate stock and operating multiple processes as improvements and changes are made more effectively across all regions*
- *A reduction in the costs of preparing / reviewing certain regulatory submission.*
- *Enhanced assurance of consistent availability of medicines to the patient."*

This third concept that emerged was as follows:

Concept 3: The concepts laid out in ICH Q9, Q10 and Q12 are not, by themselves, sufficient for realisation of the desired state and its expected benefits. Standard practical solutions that are developed in a unified manner by a stakeholder group at a senior leadership (decision-makers) level, to ensure that they can be implemented in collaborative and consistent ways within and across stakeholder segments, are the missing components for success and realisation of the desired state. Associated queries that might be worth looking into for future research could include the following:

Associated Queries:

- Even though it was based on the ISO 9001 QMS framework, could the establishment of a separate ICH Q10 PQS model specifically for pharmaceutical companies, have inadvertently moved the pharmaceutical sector away from standardising on concepts and solutions (such as those expected by ISO)?
- How could standard solutions (such as those resulting from this research study) and standard certifications of an effective PQS (such as ISO certification of a company's QMS system), *leap-frog* achievement of the vision laid out in the ICH guidances?

Indeed, the medical device industry has a long history of using and getting certified against ISO standards such as ISO 13485, *Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes* and ISO 14971, *Medical Devices – Application of Risk Management to Medical Devices*. In Europe, products sold in the European Economic Area (EEA) and the European Union (EU) are certified with a CE mark, an EU Declaration for Conformity to relevant European product directives. It's

worth the pharmaceutical industry considering the adoption of similar harmonised ISO or CE mark certifications that could drive standardisation of the PQS and realisation of its envisioned value.

Based on these hypotheses, concepts and associated queries, two final research questions crystallised; these were as follows:

- **Research Question 1 (RQ1)**: How can an effective PQS, coupled with product and process understanding, including QRM, be used to *"optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement"*?
- **Research Question 2 (RQ2):** How can the pharmaceutical industry be unified to develop and implement standard practical solutions, in collaboration with regulatory authorities, for *"effective risk-based PAC management within the PQS"*?

3.5 Research Study Design, Methodology, and Methods

Based on the underlying worldview and research questions discussed in the prior sections, and the insights gained during the course of the research, a mixed methods approach was determined to be the most suitable research methodology for this study design. And given the iterative nature of this study, it was determined that a ***transformative mixed methods*** strategy of inquiry would be optimal, as it would allow the use of both *concurrent and sequential exploratory and explanatory qualitative and quantitative* research techniques.

Section 3.4 above describes the qualitative research queries associated with each of the concepts explored in this study. Given the complexity of the research topic and consideration of the multi-stakeholder perspectives, the two central research questions RQ1 and RQ2 were intentionally designed to be broad in their inquiry so as to explore the complex set of factors surrounding the central phenomenon of drug shortages as a 'wicked problem'. It was also important to not be limited by the current state, to presume certain outcomes, or be exclusionary of potentially interconnected viewpoints. As emphasized in section 3.2.1 above, seeking holistic, interconnected system solutions

meant that a quantitative design for the inquiries would not provide the appropriate initial starting point.

Qualitative methods:

Literature review served as the starting qualitative method for this study. As described in Chapter Two of this thesis, the researcher determined where an abundant literature basis for this study was available, and where deficiencies existed in published literature, including the deficiencies that literature resulting from this research study was alleviating (e.g., the link between global regulatory complexity and inadequate continual improvement contributing to drug shortages, or demonstrating effectiveness of the PQS for PAC management).

The mixed qualitative and quantitative strategy of inquiry led the researcher to select ***focus groups*** as the predominant and overarching qualitative and quantitative research methodology, combined with surveys where deeper quantitative exploration on a specific aspect was deemed important. The *focus group* methodology served a three-fold purpose in the research study design:

1. To collect practical experiential data, insights, feedback and to facilitate an iterative review of study deliverables including the design of practical standard solutions suitable for implementation
2. To generate discussion among participants (from different stakeholder groups) to surface commonalities and divergent perspectives, to get to aligned understanding, and to generate unified positions among and between stakeholder groups on certain topics, such as the standard solutions developed via the *1VQ for PAC Initiative*. This, as described above in section 3.2.1, is at the core of *systems thinking*
3. To serve as a communication means in raising awareness and garnering support, to the extent of creating accountability and ownership of the solutions in order to ensure their practical implementation and achievement of the desired state

A combination of ***structured and semi-structured*** (i.e., open and informal though with defined objectives) *focus groups*, and ***unstructured*** *(formal or informal)* ***philosophical dialogues*** with key opinion leaders (KOLs) such as Senior Regulatory Authority Leaders or Senior Quality Leaders, all moderated or co-moderated by the researcher,

provided a balanced approach - the *unstructured philosophical dialogues* or *semi-structured focus groups* provided the appropriate flexibility and space that permitted participants to voice their genuine, unfiltered perspectives, while the *structured focus groups* facilitated the iterative development of the standard solutions that resulted from this research, or probed into specific topics in order to gain semi-quantitative or quantitative data. All of the *structured and semi-structured focus groups* were conducted with clear objectives, agendas and expected outcomes from each session. The main difference between the structured and semi-structured focus groups was the level of open-ended discussion space that was provided for exploratory vs. explanatory topics. These *structured or semi-structured focus groups* are described in Chapter Seven of this thesis. The *unstructured philosophical dialogues* occurred all through this study (such as with FDA, PIC/S and KOLs), and these are described in various chapters of the thesis as relevant to the context and content of those chapters.

Peer review of the standard solutions resulting from this research and their endorsement by Senior Quality Leaders or regulatory authorities' bodies such as PIC/S was a crucial extension of the *focus groups* methodology. It resulted in each of the resulting standard solutions being reviewed and commented on by 300-500 expert stakeholders for their iterative development before they were finalised and published; these stakeholders being the implementers, users or decision-makers for the solutions.

An unanticipated benefit of the *focus groups* and *peer review* methodology was that it resulted in creating a new stakeholder community through the *1VQ for PAC Initiative,* the Senior Quality Leaders in the pharmaceutical industry. This group was unified via this research for the first time in realising the significance and public health relevance of a topic that has been discussed for close to 20 years, yet has remained unsolved.

Quantitative methods:

Surveys were used to collect both quantitative and qualitative data on specific research questions at various points in the study. They were either administered concurrently with a qualitative inquiry, or sequentially, after exploration of a broader qualitative question. Survey conduct and survey results obtained and published during the pre-research work and this research study are described in various chapters of the thesis.

The ***structured focus groups*** also served a second purpose of gathering quantitative data where this was deemed useful in querying specific aspects of the research questions or when probing for insights that resulted from the *qualitative focus groups* or *philosophical dialogues*. Some examples of where a *structured focus group* served a *quantitative* data collection purpose included voting on, and prioritising, PAC examples for development of *1VQ for PAC* position papers, assessing the maturity of a company's change management system against the PIC/S Recommendation Paper (both described in Chapter Eight of this thesis), and gathering data from the CQOs on ICH Q10 benefits realisation.

Table 3.2 below summarises the research design, methodology and methods used to address the two research questions through each of the research phases as depicted in Figure 1.10 in Chapter One of this thesis:

Table 3.2: Research Design, Methodology, and Methods Used

Research Phase	Methodology	Methods
Phase 0: Pre-research	Concurrent and sequential mixed methods (Qualitative and Quantitative) Systems thinking-based design	• Philosophical dialogues • Semi-structured focus groups • Surveys • Peer reviews
Phase 1: Problem definition		• Literature review • Surveys • Philosophical dialogues • Semi-structured focus groups
Phase 2: Exploring the 'Wicked Problem' and Regulatory Authorities Positions		• Literature review • Philosophical dialogue • Semi-structured focus groups
Phase 3: Bringing the Pharmaceutical Industry Together – to establish *1VQ for PACs*		• Philosophical dialogue • Surveys • Semi-structured and structured focus groups • Peer review
Phase 4: Exploring and Developing Practical Science and Risk-Based Solutions		• Philosophical dialogue • Semi-structured and structured focus groups (for iterative solutions design) • Peer review

Phase 5: Application to Specific PAC Example Case Studies		• Philosophical dialogue • Surveys • Semi-structured and structured focus groups • Peer review • Case studies
Phase 6: Impacts and Future Opportunities		Suggested: transformative mixed methods that facilitate co-creation of systems-based solutions and new ways of working across stakeholders' and subsystems

After identification of the initial research methodology, the researcher applied for ethics approval from the TU Dublin Research Ethics and Integrity Committee, as discussed in the next section.

3.6 Research Ethics and Privacy

Research ethics and Integrity was approved, and all research activities were conducted in accordance with TU Dublin's Code of Conduct for Ensuring Excellence in Research Integrity (TU Dublin, no date).

Specifically, the researcher:

- Requested the senior-most Heads of Quality, the CQOs, in global pharmaceutical companies to identify participants for the focus group sessions held during the course of this study. As participants were selected and informed by their senior management to represent their respective companies in the focus group sessions, no additional consent forms were deemed necessary.
- The researcher did not (and will not) have any power over any of the involved research subjects, each of whom was selected by their respective pharmaceutical companies and agreed voluntarily to participate. The researcher did not have any influence over who the CQOs selected to represent their companies in the focus groups.
- Agendas with topics for discussion were disclosed in advance of the *focus group* sessions and any information captured from those sessions, which included outputs, outcomes, decisions and agreements were sent to all participants for their review and comments prior to finalisation; these were additionally sent to the CQOs of the *1VQ for PAC* member companies.

- Any publications that contained content developed or contributed through the *focus group* sessions were reviewed by all participants, their companies, and endorsed by the CQOs for those companies prior to publication.
- All electronic information for this study, including participant information and company information, were captured on a non-shared computer, handled and stored in a secure, password-protected location, with the password being encrypted and known only to the researcher. No recording devices were used.
- Though actively employed by Genentech/Roche, a private pharmaceutical company, neither the researcher nor her employer had any financial interest or material benefits resulting from this research study. There were no direct or indirect conflicts of interest, as the research intended to contribute to improving public health and the pharmaceutical sector as a whole.

The researcher also undertook formal Research Integrity Training sponsored by TU Dublin and received competency-based certificates for the domains of Natural and Physical Sciences and Biomedical Sciences. Those modules train researchers on their responsibilities and on how to handle complex issues that can arise while planning, conducting, and reporting on their research.

Part Two of this thesis, Chapter Four and Chapter Five, investigate drug shortages as a global 'wicked problem' and examine the responses to it from the pharmaceutical sector. This sets the stage for the next part, Part Three, which explores the positions of various regulatory authorities on the topic of this research.

Part Two: Recognition of Drug Shortages as a Global Problem and the Need for Global Solutions

Part Two frames drug shortages as a global problem, by exploring what makes it global, its detrimental consequences especially for patients, and therefore, why a response to it, and the resulting solutions must be global. It includes the following:

- An investigation into the term ‘wicked problem’, and what makes drug shortages a ‘wicked problem’ specifically through the lens of post-approval changes and in the context of insufficient continual improvement and innovation (Chapter 4).
- How regulatory authorities and the pharmaceutical industry have responded to this ‘wicked problem’ thus far (Chapter 5).

Chapter Four

A 'Wicked Problem' – Drug Shortages in the Context of Inadequate Continual Improvement and Innovation

Medical and pharmaceutical science continue to make incredible advances in discovering, developing and launching new therapies for unmet medical needs, and transform patient survival and quality of life. Delivering safe, effective, high-quality products to patients remains paramount – therefore both regulators and pharmaceutical companies must continue to strive for high standards to safeguard public health.

However, drug shortages have continued to become a growing global problem (Gray and Manasse, 2012; WHO, 2016c) resulting from a complex set of potential causes related to economic, business, manufacturing, quality, supply chain issues and increasing regulatory complexity (Birgli®, 2013; EAHP, 2018; AESGP *et al.*, 2019; ASHP, 2021). Many of these causes might even be the first of the causes (and not the ultimate root cause) if a *Five Whys* technique (Serrat, 2017) were to be applied as described in Chapter One, section 1.2.2 of this thesis Drug shortages have increased in frequency, severity and duration (Van Roey and Haxaire, 2008; WHO, 2016d; EAHP, 2018; EIU, 2018). Per the EAHP survey across 38 countries, the latest data from 2018 on the average duration of shortages in Europe was 2.2 months, with the maximum shortage duration reported being 13.2 months; in 2014 the survey showed that the maximum shortage duration had been 9.3 months. The 2018 survey also documented many examples of shortages up to 1 year, 2 years, 3 years or even longer, and it provided other statistically significant evidence that the problem of shortages has been increasing (EAHP, 2018). Over the last decade, regulators, legislators, healthcare providers and the pharmaceutical industry have made many efforts to ensure the uninterrupted supply of safe and efficacious products to patients; however, these efforts have not been effective in preventing drug shortages as can be seen by the continued high number of shortages at the pharmacy and/or patient level (EAHP, 2018; ASHP, 2021). ASHP provides data on national shortages in the US from January 2001 through June 2021 shown in Figure 4.1, and while the shortages reduced from 267 in 2011 to

166 in 2019 and to 129 in 2020 (ASHP, 2021), it is still premature to conclude this as evidence of a sustainable downward trend. A downward trend would still not be good enough for patients; the objective should be close to zero drug shortages.

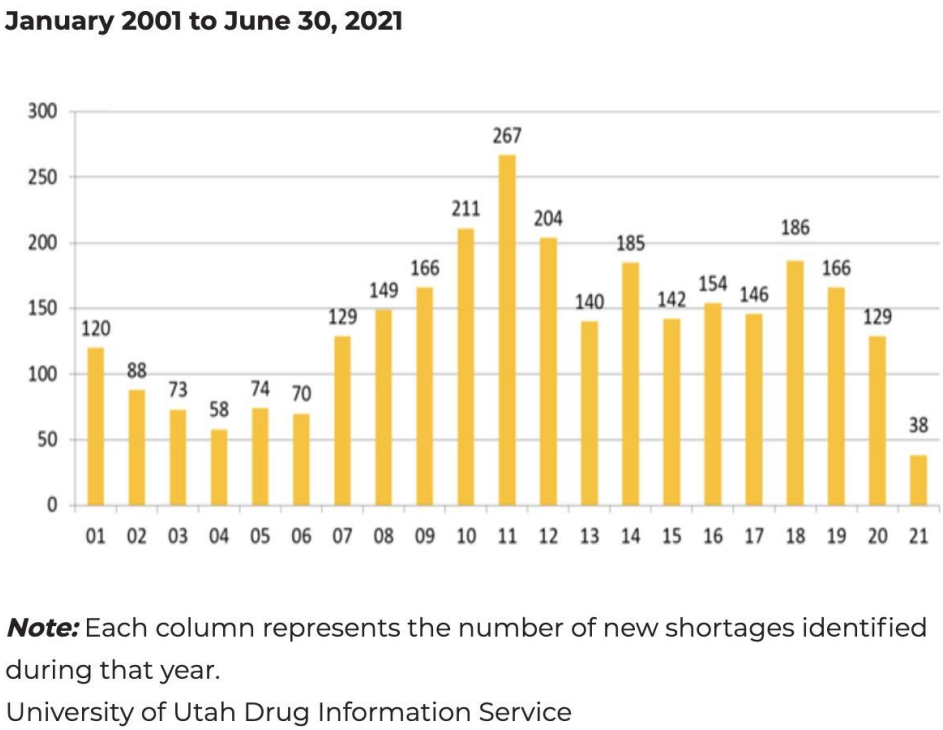

Figure 4.1: National Drug Shortages in the US (January 2001 – June 2021) (ASHP, 2021)

ICH Q9, *Quality Risk Management*, defines patient harm as:

> *"Damage to health, including the damage that can occur from loss of product quality or availability."*(ICH, 2005c)

It is not sufficient only to make safe, effective, high-quality medicines - being able to sustain a reliable, uninterrupted and timely supply of these medicines is equally fundamental to patient care. While the researcher does not have any data to corroborate, her opinion is that in the event of shortages, patients likely have to switch to an alternate if one is available in their country (alternatives are not available for many life-saving or life-sustaining drugs), or have to go without.

Timely and sustained availability of medicines to meet the needs of patients is expected by all regulatory authorities, and is also required by legislation in many countries, such as Europe's Article 81 of Directive 2001/83/EC which states that:

> *"The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply Medicinal products so that the needs of patients in the Member State in question are covered."* (European Commission, 2001)

However, in spite of significant efforts from regulators, legislators and the pharmaceutical industry, the global issue of drug shortages has yet to be resolved. The researcher contends that this is likely because solutions are still sought for mostly at a local or regional level and still inclined towards more oversight of or requirements for the industry, as opposed to seeking new, alternate and collaborative ways where stakeholders come together with a *systems-based* mindset to jointly solve a problem. This chapter provides a brief background on drug shortages and its context and relevance for this research study.

4.1 Exploring a 'Wicked Problem'

In the 21st century healthcare environment, patients should expect that medicines have the right level of quality, and that they are safe, effective and available. Yet there are an increasing number of stock-outs for medicines, mostly antimicrobial agents, preventive medicines (vaccines), and oncology medicines, including critical medicines (EAHP, 2018). In the US, shortages for sterile injectables have remained high, ranging from 39-73% of injectable and non-injectable medicines (ASHP, 2021). Though there is no harmonised definition or classification for critical medicines, as the importance of a product may vary by country based on factors such as availability of alternate medicines, disease situation, national control programs, etc., the EMA identified two criteria for defining a product as critical: therapeutic use (i.e., it is integral for treatment or prevention of life-threatening or irreversibly progressive disease or without which public health would be severely harmed) and availability (of alternatives) (EMA, 2016).

As the researcher explored the topic of drug shortages in depth, it became evident that it is a highly complex issue that could not be solved only by pharmaceutical companies and regulators; indeed, even defining the problem and its scope was difficult due to the many interdependencies it had across economic, business, supply chain, policy, regulatory and legislative considerations.

In 2016, Vinther in an article published in the PDA Letter contended that drug shortage is a ‘wicked problem’ (Vinther, 2016). This led to the researcher exploring the definition and examples of a ‘wicked problem’, including learnings from other ‘wicked problems’ that could be leveraged to solve the drug shortage situation.

As noted earlier, a ‘wicked problem’ was first defined as a problem highly resistant to solutions, by Rittel and Webber in 1973 (Rittel and Webber, 1973). These are highly complex problems that cannot be well-defined, do not have easily defined solutions, and cannot be solved by any one group of people. Examples of wicked problems include climate change, obesity, poverty, hunger, sustainability and, biodiversity loss.

With the increasing dialogue across the healthcare sector on pricing and access (Birgli®, 2013; Woodcock and Wosinska, 2013; Stomberg, 2016; WHO, 2016c) for the healthcare sector, and recognising that the problem is highly complex and highly resistant to solutions, the researcher asserts that affordable global access to medicines is indeed a ‘wicked problem’. This chapter describes the characteristics that make drug shortages a ‘wicked problem’, and why in spite of sincere and focused efforts by different stakeholder groups, it has yet to be resolved. It also expands on the complexity of stakeholder groups and where collaborative and complementary efforts might be essential. Finally, it delves into the global regulatory complexity that exists and discusses how this might be an aggravating factor in addressing the ‘wicked problem’ of shortages. This component of the research set the foundation and led to a deeper exploration into one of the many contributing factors to drug shortages - namely the global complexity and long lead times for continual improvement and innovation in the manufacturing, testing and supply of products to patients. Indeed, it was found that this complexity eventually, even if indirectly, resulted in the unintended and undesired consequence of drug shortages.

During the course of this research the COVID-19 pandemic presented an unexpected serious crisis that challenged pharmaceutical companies and regulators alike in making life-saving decisions for patients in unprecedented ways. The global impact of COVID-19 has demonstrated that diseases know no borders, and solutions to fight such diseases must be global. Opportunities to learn from and adopt new ways of working have

emerged from the crisis; these should be integrated into transforming how patient needs are met post-pandemic, by making products available with the highest sense of urgency.

4.2 The Characteristics of Drug Shortage that Make it a 'Wicked Problem

Drug shortages present all the characteristics of a 'wicked problem' that Rittel and Webber articulated as depicted in Figure 2.5, Chapter Two of this thesis, and as first described by Vinther in an article in 2016 (Vinther, 2016). The following aspects make drug shortage a 'wicked problem':

- **Every problem is unique and is difficult to clearly define**:

  For drug shortages: in spite of attempts by EMA and WHO (WHO, 2016d), there is still not a single unified definition of a shortage that could be agreed upon by all stakeholders. WHO identified at least fifty-six known definitions of shortages - depending on what aspect of the supply chain they addressed (e.g. at the manufacturing level, distribution centre level, pharmacy level, or patient level), or based on timeframes or durations, or varying levels of specificity, or interchangeable terms (e.g., shortage, unavailability, disruption of supply, interruption of supply etc.), or based on the demand side of the system (e.g., at healthcare facilities) (WHO, 2016d). The criticality and patient impact of a shortage varies, and therefore the level of risk, nature of solutions, and attention to resolution could vary broadly. Stakeholders may agree on the nature of the problem and the importance of addressing it, but they may not always all agree on how to solve it. This is evident through the extensive and ongoing discussions on drug shortages that have taken place over the years as described in Chapter Five of this thesis.

- **Often the problem is multi-causal with interdependencies and interconnectedness**:

  For drug shortages: the causes can range across economic (e.g., price cuts, spend reductions, reference pricing, payment delays, tendering), business (e.g., reduced product introductions, parallel distribution, tight payment terms, market access and withdrawals, market quotas) and manufacturing and supply chain (e.g., manufacturing or quality issues, just-in-time supply chain, legislation change, channel strategy) (Birgli®, 2013; AESGP *et al.*, 2019). Often the cause-effect

relationship is difficult to determine or demonstrate and every drug shortage situation can be considered a symptom of another problem. It is also possible to explain the drug shortage problem and its causes in many different ways, sometimes such that different stakeholders have a different understanding of the problem, its causes, and possible solutions. Each shortage event is different and can present a unique set of causal events with varying interdependencies in each country or region, and therefore may need to be dealt with differently with different stakeholder groups, in different countries. Additionally, there is an interconnectedness across various issues and causal events which makes each stakeholder view their understanding of the problem and its solution as the correct one, based on the objectives of their organisation. The pharmaceutical industry (via the *1VQ for PAC Initiative*) has stated that the global regulatory complexity associated with medicines is a key contributing cause for drug shortages (Vinther and Ramnarine, 2019a), while regulators often take the position of manufacturing and quality issues as a key cause for shortages (EMA, 2012; FDA, 2019). Each stakeholder tends to see and act to solve the problem in a linear manner from their own perspective.

- **The problem has multiple stakeholders, cannot be solved by any one group:**
  Solving a wicked problem is rarely the responsibility of one stakeholder. Often the stakeholders are dispersed with conflicting agendas such that getting to a shared understanding of the problem itself becomes difficult.

  For drug shortages: manufacturers, MAHs, regulators, suppliers, wholesalers, distributors, hospitals, pharmacies, patient advocacy groups, and policy makers all play a role, depending on the nature and extent of the shortage. Addressing the issue of shortages therefore, must cut across a range of organisational and disciplinary boundaries. Often adequate communication channels do not exist between and across all these stakeholder groups, making it extremely hard to coordinate, design and implement joint, collaborative or integrated solutions. The need to work across stakeholders has been recognised, for instance by WHO (WHO, 2016c) EMA (EMA, 2013, 2015a, 2018) and the Economist (Boshnakova, Karnad and Pannelay, 2017). Though the various stakeholders have attempted to address the problem of shortages, most have assessed it either only locally or regionally, from their specific perspective (e.g., regulators within their jurisdiction, pharmaceutical companies

from an industry viewpoint, or supply chain players from their perspective), or with a subset of other stakeholder groups (EMA, 2018; AESGP *et al.*, 2019). In spite of the various EMA multi-stakeholder workshops, the opportunities to design joint solutions did not materialise to the extent needed, as evidenced by the continued efforts to solve the shortage issue. With the EMA Drug Shortage Inter-Association Task Force's body of work, described in Chapter Five, section 5.3.3 of this thesis, the collaboration was limited to pharmaceutical industry association groups; it did not extend to joint solutions with the other stakeholder segments and therefore, in the researcher's opinion, fell short of what was truly needed to address this 'wicked problem'. Additional attempts should be made to set up multi-disciplinary, cross-stakeholder efforts similar to the ones EMA (EMA, 2013, 2015a, 2018) and WHO (WHO, 2016d) attempted, but broader, bolder, more inclusive, innovative and disruptive in its scope and vision. To this end, instead of discussing what other stakeholder groups could do the *1VQ for PAC Initiative* co-led by the researcher and described in Chapter Seven of this thesis, focused on actions the pharmaceutical industry could take without waiting for other stakeholders to do their part.

- **The problem is often not stable**:

  For drug shortages: managing through a shortage situation can be highly dynamic and sometimes unpredictable, making it difficult if not impossible at times, to lay out a clear, well-structured plan in advance, based on past learnings and experiences. Even where a plan may have been put in place proactively, the researcher's experience has been that it was typically not straightforward to execute as designed, because of the diversity of the causes, implications, and varying potential solutions for each shortage situation. Additionally, because every shortage situation was often unique with typically no precedents, prior experience with a previous shortage offered little value if any, in resolving a new shortage event. Opportunities to learn by trial-and-error tend to be limited at best, making any solution a 'one-shot' operation, as termed by Rittel and Webber. This became particularly evident with the COVID-19 pandemic where exceptional processes such as EU's Exceptional Change Management Process (ECMP) or FDA's Emergency Use Authorization (EUA), described later in Chapter Ten, section 10.1.1 of this thesis, had to be put in place or activated as the regulatory frameworks for PAC

management were not agile enough to adapt to sudden changes in medicine demands.

- **No clear solution to the problem**:

  For drug shortages: this problem has existed for 15+ years and has been acknowledged as a growing issue for almost as long. If a simple solution were obvious and possible, it would have been implemented already. It is clear that given each shortage problem can be unique, a solution that could resolve a shortage in one situation might not work in another; hence the term 'one-shot operation' used by Rittel and Weber, meaning there is no opportunity to learn by trial-and-error. Depending on the causal events, criticality, level of impact, local requirements, possible mitigating or aggravating factors, the solutions for a shortage may vary greatly. Solutions are not right or wrong, rather they are better or worse; and the determination of better or worse becomes a judgment call that is based on the perspective of one stakeholder versus another. There is usually no ultimate or immediate test of the 'goodness' or 'effectiveness' of a solution for the wicked problem of shortages. In fact, it is usually impossible to find a single solution for a 'wicked problem' like shortages, that meets the needs of all stakeholders. The problem must be addressed globally, but the solutions are unlikely to be global, in terms of 'one size fits all'. It can also take a long time to determine whether a solution has made things better or not. There is no way to know if a solution is final and therefore, the search for a solution cannot stop (also called by Rittel and Webber as the 'no stopping rule' (Rittel and Webber, 1973)). Given these challenges, the effort to find solutions needs to be elevated to another level and *systems thinking* needs to be applied, as has been initiated by this research including the *1VQ for PAC Initiative* described in Chapter Seven of this thesis.

- **Attempts to address the problem often leads to unforeseen consequences**: Each solution can have ramifications that may extend beyond the anticipated or foreseen implications. Some consequences may be irreversible and may even manifest over an extended period of time.

  For drug shortages: the supply chain is global but supply management and oversight at the regulatory authority level is still national. An example is legislation or regulatory requirements being set by each country or region to deal with the issue of shortages within their specific scope – this has led to an exponential increase in

regulatory complexity for global pharmaceutical companies which then struggle to meet and comply with all local and regional expectations that vary greatly by country or region, in order to make product available. Solving a drug shortage in one country might lead to issues in other countries. The unintended consequences of a regulation being put in place might not be recognised until years later. As another example, the EU variations regulations while well-intended and clear in their objectives, caused a significant discord and challenge during the development of ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*. After extensive discussions, an allowance for regional requirements had to be included in the published ICH Q12 guidance as follows, leading to a widespread concern that the guidance would not help reduce the global regulatory complexity to the extent needed:

> *"Use of Q12 tools is not intended to change the responsibilities for the holder of the referenced information, the MAH or the regulatory authority. For example, the holder of the referenced information has a responsibility to report relevant drug substance changes to the MAH referencing their submission, so that the MAH can assess the impact of the change and report any related changes to the approved MAA, as necessary and per regional requirements."* (ICH, 2019)

Significant resources and effort within the supply chain and regulatory functions in a pharmaceutical company need to be dedicated simply to navigate and manage through the complexity presented by implementation of local and regional solutions, without adequate consideration of the global impact. The complexity has become severely constraining for manufacturing and supply chain operations (Vaccines Europe, 2016). Instead of improving the availability of medicines, it has been getting in the way of making products available, as evidenced by the conflict between the initial draft of ICH Q12 and the EU variations regulations. With the EU variations regulations being legally binding, the ICH Q12 language had to be modified in order to avoid being contradictory to those regulations.

- **The problem is socially complex**:

  <u>*For drug shortages*</u>: beyond the direct implications for patients, the multi-causal nature and multi-dimensional impacts associated with shortages, makes it a problem that affects society's overall well-being. Because the players involved are so widely dispersed, and because society's infrastructural or organisational elements are not designed for those players to come together in solving the issue in a collaborative or

integrative manner, the problem is socially complex and difficult to handle in spite of all stakeholders desiring to invest in solving the problem. An example is related to the distribution of COVID-19 vaccines – according to *Our World in Data*, that focuses on *research and data to make progress against the world's largest problems*, as of 9-September-2021, 41.3% of the world population has received at least one dose of a COVID-19 vaccine, but only 1.9% of people in low-income countries have received at least one dose of a vaccine (Our World in Data, 2021). Effective inclusion and involvement of patients and patient advocacy groups in solving the drug shortage problem is further needed.

- **Solutions to the problem involve changing behaviours**:

  Traditional ways of working or solving a problem most often do not work for wicked problems. Seeking alternate, new and often transformative ways of working is often necessary.

  For drug shortages: working beyond and across organisational boundaries, with a *systems thinking* worldview is essential to solve this problem as described in Chapter Three, section 3.2.1 of this thesis. Innovative, adaptive and flexible models are needed that require everyone involved in managing shortages to change their mindset and behaviours. This also includes having the willingness and courage to cross organisational and disciplinary boundaries, establish processes, resourcing, infrastructure and tools that are capable of cutting across and beyond local or regional requirements, and giving up local or regional practices for the sake of the greater global good. This requires building trust, transparency, and establishing or opening up communication channels between stakeholder groups where they might not exist. As an illustration, when patients in a country such as Vietnam or Kenya are impacted by a shortage, stakeholders in other countries such as the US or Germany would need to care and work with them to make the medicine available to patients in Vietnam and Kenya, just as much as they would to make it available to patients in their own countries. For behaviours to change, the solutions need to be driven and owned by those whose behaviours must change. This is not an easy mindset barrier to overcome, and tools beyond the traditional ones of legislation, regulations, local policies etc., are needed to drive such cooperative behavioural changes.

- **The problem can be resistant even to policy solutions**:

For drug shortages: the problem is global, but in the current state, policy approaches are typically national or regional. The supply chain will likely always be driven by economic and geopolitical factors. It is important for governments and policy makers to recognise and advocate the need for policy changes first at a country or regional level and then at the global level. Short-term solutions are less likely and commitment must be made towards longer-term strategies and sustained efforts, in spite of uncertainties and the inability to prove effectiveness of any actions taken in the short to medium term. A good and recent example is the PQKMS strategic initiative launched by ICMRA as mentioned in Chapter One, section 1.2,1 and described in Chapter Six, section 6.5 of this thesis. Policy makers also need to be open to taking learnings from others, and adopting innovative measures that others might have implemented. Failures in policies should be viewed as learning points resulting in a willingness to learn, adapt and try something different.

As described above, drug shortages demonstrate the characteristics of a 'wicked problem', thus one should not expect this global issue and 'wicked problem' to be solved in the near-term no matter how intensive the efforts and investment might be. It is for this reason, in spite of the right intent and efforts from various regulatory authorities such as EMA, FDA, WHO and the pharmaceutical industry, society and patients as a whole have continued to struggle with unreliable medicines' access. Dialogue, shared understanding, collaboration and shared commitment from all stakeholders are essential to addressing the 'wicked problem' of shortages and achieving the common objective of ensuring reliable and sustainable availability of medicines for patients.

4.3 Relevance of Drug Shortages to this Research Study

Most pharmaceutical companies have been challenged with managing drug shortages, many of which may be due to causes beyond the scope and control of the MAH (Birgli®, 2013; AESGP *et al.*, 2019). It is the researcher's belief that drug shortages due to manufacturing and/or quality issues can and should be proactively anticipated and prevented by manufacturers and MAHs. In general, drug shortage management has

primarily been reactive in that, companies and regulators do not typically have drug shortage plans and therefore deal with shortage crises as and when they arise. This severely limits the options that might be availed of to mitigate a shortage situation, simply because of time pressures, a lack of visibility, poor communications and timely access to all stakeholders and solutions that might be possible to resolve a shortage. Several parallels can be drawn between *drug shortage prevention planning and business continuity planning, and between drug shortage response planning and crisis management planning* – drug shortage prevention planning would enable the prevention and reduction of shortages, and also lead to better and faster response in the event of a shortage, with quicker recovery to normal state.

The researcher proposes that an underlying premise to make this possible is for companies to effectively use and apply QRM as intended by ICH Q9, to proactively identify, assess and control risks in their manufacturing and supply operations before the risks materialise and impact a company's ability to reliably supply products to patients. Furthermore, the researcher asserts that QRM and KM must be the foundational basis for such shortage prevention and response planning. The limited guidance in ICH Q9 on addressing product availability issues, resulted in Dr Kevin O'Donnell developing in 2018 a proposal to revise ICH Q9 in order to expand on the importance of using QRM to address product availability risks among other topics (ICH, 2020). An ICH Q9 EWG with O'Donnell as the Rapporteur is currently working on this revision to ICH Q9.

As stated in Chapter Two, section 2.2 of this thesis, from 2012-2014, the researcher led the development and publication of PDA Technical Report 68, which is further described in Chapter Five, section 5.3.4 of this thesis. That Technical Report identified aging (or obsolete) facilities, equipment and technology as one of the causes of drug shortages, because older assets may not be able to meet current standards and performance expectations to deliver the required product quality attributes, or simply because they breakdown often leading to quality issues. Continual improvement and upgrades to facilities, equipment, processes and methods lower the risk of failures and their resulting quality issues. The Technical Report emphasized the importance of continual improvement and innovation as essential for lifecycle management. It also acknowledged that continual improvement can be slow with very limited or no

incentive for companies to innovate and improve because of the global regulatory complexity for the approval of changes, even when they reduce potential risks to product quality, patient safety and drug shortages.

As a follow-on to the work on PDA Technical Report 68, the researcher explored the current global PAC landscape and what could be done to expedite PACs even though regulatory processes may take a long time to harmonise. In the report, the researcher articulated ways that companies could use enhanced and prospective science and risk-based approaches for specific types of changes to expedite approval and implementation of PACs. It was further proposed that a company's PQS should be used to manage more changes in order to implement changes faster to mitigate the risks of drug shortages caused by aging facilities, equipment and processes.

All of this formed the basis for this research study into the use of an enhanced science and risk-based approach and an effective PQS for the management of PACs. The subsequent parts of this thesis present the researcher's view on why regulatory authorities and the pharmaceutical industry need to develop standard solutions in this area and the interactions that are important between these two stakeholder groups. Those standard solutions when implemented, should result in more effective and more timely PAC management in order to ensure reliable and timely supply of quality medicines to patients.

4.4 Complexity of the Global Regulatory Landscape and Why it Matters?

The global regulatory landscape has continued to become increasingly diverse and complex over the past 15 years, with regulatory authorities further developing their national and regional regulatory frameworks, becoming more advanced in their requirements, and increasing their level of expectations from MAHs. Getting a PAC approved globally by all countries where a product is filed takes a long time, sometimes several years. The regulatory framework for PAC management is simply not capable of reacting with agility to implement changes that enable continual improvement and innovation even where such changes can reduce risks to patients. In general, the increased rigor and scrutiny is well-intentioned and justified given the diversity and

complexity of pharmaceutical advances, and the range of maturity in quality mindset, systems and processes that regulatory authorities usually experience across the pharmaceutical industry. This causes them to have to sometimes establish requirements or regulations that are aimed at the lowest common denominator as opposed to ones that reflect more advanced positions. An example of this is animal testing being required in China to release every batch of product even when better test methods might already be a part of the product control system.

A useful research study which illustrates this complexity was carried out by the Economist Intelligence Unit (EIU); it is discussed in section 4.4.1 below, giving some understanding of the current regulatory landscape, and the implications it might present in the context of drug shortages and PACs.

4.4.1 Economist Intelligence Unit (EIU) Drugs Shortages Research

In 2017, the EIU published a report on *Cancer Medicines Shortages in Europe* (Boshnakova *et al.*, 2017). The EIU, established in 1946, helps businesses and organisations understand how the world is changing, what risks and opportunities are present, and how to manage them. EIU Healthcare does this through customised and evidence-based research, market intelligence and analysis to help healthcare organisations deliver better value products and services, and manage sustainably and successfully for the future.

This independent research by the EIU on cancer medicines shortages in Europe, commissioned by the European Society for Medical Oncology (ESMO), explored current European policy and regulatory frameworks for medicines supply. It resulted in EIU making six policy recommendations for countries in Europe to prevent and manage cancer medicines' shortages. These recommendations were in line with FDA and EMA's work on drug shortages and were as follows (Boshnakova *et al.*, 2017):

1. Introduce legislation for early notification requirements for medicines shortages
2. Establish strategic plans for medicines shortages
3. Develop catalogues of shortages
4. Develop essential medicines lists and assess the risks for shortages

5. Introduce incentives for production infrastructure improvements
6. Establish procurement models designed to prevent medicines shortages

They published an additional research report in 2017 titled *Addressing Medicine Shortages in Europe* (Boshnakova, Karnad and Pannelay, 2017) that was supported by Medicines for Europe. Development of policies that ensure maintenance of fair economic conditions was noted as key for reduction of shortages. It also emphasized the importance of all stakeholders – competent authorities, manufacturers, wholesalers, parallel distributors, pharmacists, clinicians and patients, in together creating a shared vision and taking collective actions to address the problem of drug shortages. The research involved interviews across this broad segment of stakeholders, including the generic and innovative pharmaceutical industry representatives, and patient groups. The research identified several actions that reiterated the importance of having a common definition of medicine shortages, implementing early notification requirements, and establishing a system that promotes transparency of shortages at a national level. One of the actions it specifically identified was *"Enhance the efficiency of regulatory procedures and implement fast-track processes to mitigate acute medicine shortages."* However, it was interesting that the topic of global regulatory complexity did not feature in the EIU research.

Global regulatory complexity had started to emerge as a topic worthy of deeper exploration in the context of the researcher's drug shortages work with the PDA PAC iAM^{SM} Task Force, as described in Chapter Seven, section 7.1 of this thesis. The researcher was keen to understand why it did not feature anywhere in the EIU report, whether the EIU had researched the topic of global regulatory complexity as part of their work, and if so, what were its findings. To this end, the researcher and Vinther contacted the authors of the EIU report, Anelia Boshnakova (Senior Information Specialist and the main project researcher), Annie Pannelay (Principal for Healthcare and senior advisor for the project) and Aditi Karnad (Senior Healthcare Analyst) to understand the scope and extent of their work. EIU acknowledged that since their scope was focused on the EU, which has a common regulatory framework for all companies in the EU, they had not delved much into the topic of global regulatory complexity. EIU also acknowledged the high complexity and multi-faceted nature of the drug shortages problem, true to the characteristics of a 'wicked problem', and they agreed to research

the link between global regulatory complexity and drug shortages, as a new and independent segment of their work on drug shortages.

The researcher and Vinther developed a proposal for PDA to commission the EIU to perform an independent research study into global regulatory complexity, and that study was initiated in late 2017, continuing through the first half of 2018. The hypothesis for that research was that:

> *Complex regulatory processes that are long and can vary greatly between countries, can result in long lead times to implement variations, thereby creating numerous challenges for sustaining the supply of medicines.*

The objective of the study was to explore the link between complexity and diversity of regulatory requirements for PACs and drug shortages. The EIU research included a literature review and interviews with representatives from academia, industry, regulatory authorities, international organisations and non-governmental organisations. It assessed the current global regulatory landscape and varying regulatory requirements, the state of regulatory harmonisation and convergence initiatives, hurdles to achieving regulatory change around shortages, and opportunities to improve regulatory harmonisation and convergence. The published report (EIU, 2018) listed the following six key findings:

1. Medicines and vaccines shortages are a global problem affecting rich and poor countries alike
2. Causes for shortages are complex, multi-faceted and not well-understood
3. The study found little evidence for the existence of a direct correlation between the global complexity of regulatory requirements for post approval changes and shortages; however, it indicated that the complexity could be an aggravating factor that delays or hinders mitigation actions
4. There is a universal agreement that regulatory convergence and harmonisation are beneficial to all stakeholders
5. Trust and strong political will are required for harmonisation and convergence initiatives to succeed
6. Finding a permanent solution for shortages is critical for achieving global health goals

These EIU findings were not entirely unexpected given drug shortages are a 'wicked problem' and therefore, it is difficult to draw a direct cause-effect correlation between global complexity for PACs and drug shortages. The position of various regulatory authorities and the complexity of the global regulatory landscape is discussed in Chapter Six of this thesis.

4.5 Drug Shortages through the Lens of Post-Approval Changes

The EIU research, as discussed in section 4.4.1, resulted in the report *Medicine and Vaccine Shortages: What is the Role of Global Regulatory Complexity for Post Approval Changes?* (EIU, 2018). The research reiterated that there is considerable regulatory variance, with different countries and regions having their own requirements, classification systems, reporting categories and processes for review and approval of PACs. This results in manufacturers having to submit multiple applications, to different countries or regions for a single PAC, even when the data and scientific basis for the PAC remains unchanged. Sometimes, different countries require submission of different data and scientific requirements for the same PAC in some cases, and this can even mean, for example, additional animal studies or clinical trials (Vaccines Europe, 2016). It is difficult to explain logically why some countries can accept and approve a PAC without additional studies or trials, while others require them, even though the risk of the PAC to product quality and/or patient safety remains essentially unchanged, irrespective of the country.

The EIU research study (EIU, 2018) included a comparison of approval timelines in different countries, and found it ranged from 30-90 days for a major change in the European Union (Lokesh, Gupta and Belagoankar, 2015) to 730 days in South Africa (Chorley, 2014). The study found that such varying requirements and approval timelines contribute to making the global regulatory processes highly inefficient, and result in complex, time-consuming, difficult to manage PAC processes for manufacturers (Vaccines Europe, 2016). It can also significantly increase challenges when trying to mitigate a shortage as varying regulatory timescales and complexities increase approval lead times.

The EIU report noted that the global complexity increases the risk of errors, can result in non-compliance with regulatory requirements, and presents a barrier to innovation and continual improvement, while also increasing the burden on MAHs in terms of time, resources and costs to develop and submit multiple applications for each country for the same change. Therefore, while solving the global regulatory complexity by itself will likely not eliminate drug shortages, it can address and simplify several issues that directly or indirectly contribute to drug shortages.

The focus of this PhD research study is not as much to solve the problem of a lack of global regulatory harmonisation or convergence, as it is to explore even in the current complex global environment, the actions that pharmaceutical companies and regulators could take to reduce the drug shortage problem through unified leadership-sponsored science and risk-based approaches, as described in Part Four of this thesis.

This chapter described what makes drug shortages a ‘wicked problem’ and it expanded on the available evidence which reinforces this assertion. The next chapter then shifts the focus for the remainder of this thesis to what then has been done, what is in progress, and what can be done even further to address this ‘wicked problem’.

Chapter Five

Responding to the 'Wicked Problem'

A patient's reality due to a drug shortage underscores the fact that, while improving patient care through medical advances and assuring high quality medicinal products are important, being able to sustain reliable, uninterrupted and timely supply at all times, is even more fundamental to patient care and protection. As discussed previously in Chapter Two, section 2.2 of this thesis, the causes of drug shortages are varied and regulators have been particularly emphatic that drug shortages caused by manufacturing and quality issues are common and must be addressed. The researcher proposes that by exploring in detail why manufacturing and quality issues occur, clear evidence would emerge indicating that these issues are often exacerbated by 3 key factors, namely:

- a lack of investment in current technologies and facility upgrades
- insufficient proactive end-to-end supply chain risk management
- regulatory hurdles to PACs that limit innovation

Investing in state-of-the-art technologies and facilities, building resilience into the supply chain, and improving interactions between the pharmaceutical industry and regulators, are key elements to ensuring reliable supply of safe, effective, high-quality medicines to patients.

The urgency to address these key elements and develop sustainable solutions has resulted in increased collaboration opportunities and much-needed dialogue between regulators, legislators, healthcare providers and the pharmaceutical industry over the last 5-7 years. The common unifying objective has been preventing drug shortages to ensure uninterrupted supply of safe, effective, high-quality products to patients. To achieve this, all stakeholders must explore and develop solutions that will serve the best interests of patients, and bring patient care to a reliable, sustainable and improved state. It is not an easy challenge to overcome, but for patients, this a non-negotiable especially in the case of life-saving, life-sustaining, or medically necessary products.

This research study focuses specifically on the relationship between the pharmaceutical industry and its regulators, with particular emphasis on developing solutions which can

be implemented by the pharmaceutical industry. Thus, this chapter describes the response from regulatory authorities and pharmaceutical companies to the concerning increase in the 'wicked problem' of drug shortages. PDA Technical Report 68 being fundamental for the exploration of the topic, is also discussed in this chapter.

Before embarking on the details of research-related activities, it is first useful to explore the role of regulatory authorities in the context of drug shortages and their relevant activities thus far in responding to drug shortages.

5.1 The Role of Regulatory Authorities in the Context of Drug Shortages

Less than10 years ago, neither the investigation and management of drug shortages nor addressing product supply issues were a core or routine activity for many regulatory authorities. Typically, the primary responsibilities of many regulatory authorities focused on the licensing of medicines, the inspection of manufacturers, MAHs, and wholesalers, carrying out pharmacovigilance activities, etc. Their responsibilities did not generally extend to the management of product supplies, nor to resolving supply shortages. Consequently, the legislation and regulatory processes for drug shortage-related work was underdeveloped or in some cases, not existent. With the increased occurrence of drug shortages within the last decade, the role and involvement of regulatory authorities in resolving and responding to shortages has become more prominent, given that the primary objective of regulatory authorities is to protect patients by ensuring the *availability* of safe, effective, high-quality medicines.

This increase in drug shortages and product supply issues highlighted the importance of early interactions between a pharmaceutical company and relevant regulatory authorities when shortage issues arise or are likely to arise. In instances where a potential supply disruption may have patient impact (e.g., for life-saving, life-sustaining or medically necessary products), regulatory authorities must be involved as early as possible in the various aspects of drug shortage management and response activities. In many countries, it is a regulatory and/or legal requirement that regulatory authorities are notified by a MAH of a potential drug shortage as soon as one becomes apparent; some regulatory authorities even go to the extent of specifying the notification timelines.

Some relevant GMP requirements are provided in the EU directives (European Commission, 2001), the EU GMPs (EudraLex Vol. 4, 2021), and US FDASIA laws (FDASIA, 2012).

Early and timely notifications have had a positive impact in reducing shortages, by enabling manufacturers and regulatory authorities to jointly take steps to reduce supply disruption (FDA, 2011; European Commission, 2012; EMA, 2019). As identified by the researcher in PDA Technical Report 68, because the primary goal of regulatory authorities is the protection of patient health, they should be actively involved in any of the following for management of a drug shortage issue:

- Providing oversight of how a company is managing a particular shortage situation
- Reaching out to other manufacturers that produce the same or alternate products to ask them to increase the supply of their product to mitigate the shortage issue
- Working across various stakeholder groups i.e., patients, healthcare professionals, government agencies that purchase medicines etc., in order to coordinate actions and responses to a shortage. A pharmaceutical company usually may not have direct access to or any authority over these stakeholder groups, and this is where a regulatory authority can play a significant role
- Ensuring that a company has identified adequate corrective actions to not only mitigate the shortage at hand, but also prevent a similar recurrence in the future
- Contributing and enabling an environment and processes that ensure robust supply chains capable of preventing and rapidly responding to drug shortages

The researcher's experience is that regulatory authorities typically take a risk-based approach to addressing shortages that may have an impact on patients in the near or longer-term. Not all shortages impact patients; many may have no impact at all, and there is usually no need for regulatory authorities to become involved in those. Notwithstanding this, regulatory authorities and the pharmaceutical industry both have an interest in understanding the causes of drug shortages, and proactively identifying and taking preventive actions.

Identification of which shortage issues may impact patients and which may not, requires careful analysis on a case-by-case basis; additionally, the situation and its mitigating

actions may vary from country to country. Robust risk assessments based on current knowledge of manufacturing and supply processes, understanding of the root or aggravating cause(s) behind a specific shortage issue, and active and timely dialogue with regulatory authorities can facilitate risk-based evaluations and decision-making by the pharmaceutical company and the applicable regulatory authority. These can also help activate collaborations across appropriate stakeholder groups to quickly resolve a shortage situation and minimise impact to patients.

5.2 Regulators' Response to Drug Shortages: Overview of EMA, FDA and WHO Activities

This section reviews at a high level, the activities (primarily prior to the COVID-19 pandemic) that key regulatory authorities such as EMA, FDA and WHO initiated over the last 10 years as the issue of drug shortages increased. Since this research study was scoped for the pre-pandemic state and because the pandemic is still ongoing with learnings, continuing to emerge, regulatory authorities' responses to mitigate drug shortages during the COVID-19 pandemic are not included in this section.

Nevertheless, key insights gained thus far from the pandemic in context of regulatory flexibility provided by regulatory authorities for PAC management to mitigate drug shortage of COVID-19 medicines, is indicative of progress in the science and risk-based direction this is being advanced by this research including the *1VQ for PAC Initiative*; therefore, the pandemic-related learnings and insights are discussed in Chapter Ten, sections 10.1 and 10.2 of this thesis.

5.2.1 EMA Activities

In November 2012, EMA published an ***EMA Reflection Paper*** (EMA, 2012) on medicinal product supply shortages caused by manufacturing or GMP compliance problems and an ***Implementation plan 2012-2015*** (EMA, 2015b). The Reflection Paper focused on lessons learned, and identified 10 short- and 3 mid-term actions that could be taken for the management and minimisation of supply shortages arising from manufacturing problems and quality defects. The short-term actions included establishing a catalogue of Centrally Authorised Products (CAPs) requiring coordination at an EU level, maintaining a public catalogue of current CAP shortages,

assisting the EU regulatory authorities known as National Competent Authorities (NCAs) with dealing with certain shortages at the EU level, establishing a procedure for handling shortages due to quality defects and manufacturing problems, clarifying reporting requirements for supply restrictions, information sharing on best practices and risk management strategies, and raising awareness and stimulating industry response towards improvement. The mid-term actions focused on better and proactive risk management by MAHs and facilitating a risk-benefit evaluation in the event of a shortage; the latter was intended to balance between the potential risk of a product defect versus risk to product availability. The Implementation Plan detailed the expected deliverables and owners for implementation of the aforementioned short- and medium-term actions. Two of the outcomes of the EMA Reflection Paper and its Implementation Plan were that relevant stakeholders were brought together and a Call to Action was issued to pharmaceutical industry associations. The Call to Action resulted in the establishment of a ***pharmaceutical industry Inter-Association Task Force***, which comprised of representatives from the pharmaceutical industry professional associations and trade associations. The researcher was invited to be a core member of this Task Force because she was leading the PDA Drug Shortage Task Force and because of her QRM and risk-based application experience and together with Vinther, she represented PDA on the Inter-Association Task Force. The composition of this Inter-Association Task Force, its charter, and the body of work commenced and completed is elaborated upon in section 5.3.1.

5.2.2 FDA Activities

During the period January 2010 to September 2011, FDA had successfully prevented 137 drug shortages (FDA, 2011); however, prescription drug shortages continued to threaten the health and safety of the American public. On 31-October-2011, President Obama signed an Executive Order (The White House, 2011) directing the FDA to:

- *"take steps that will help to prevent and reduce current and future disruptions in the supply of lifesaving medicines."*
- *"use all appropriate administrative tools including authority to interpret and administer the reporting requirements in 21 U.S.C. 356c, to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life supporting or life sustaining, or that prevent debilitating disease."*

- *"take steps to expand its current efforts to expedite its regulatory reviews, including reviews of new drug suppliers, manufacturing sites, and manufacturing changes, whenever it determines that expedited review would help to avoid or mitigate existing or potential drug shortages. In prioritizing and allocating its limited resources, the FDA should consider both the severity of the shortage and the importance of the affected drug to public health."*
- *"communicate to the Department of Justice (DOJ) any findings that shortages have led market participants to stockpile the affected drugs or sell them at exorbitant prices."*

In conjunction with the Executive Order, the FDA also accelerated its focus and efforts on addressing drug shortages in the US. In 2011, it published a comprehensive review on its approach to managing drug shortages, *A Review of FDA's Approach to Medical Product Shortages* (FDA, 2011). The report concluded that drug shortages were a complex problem resulting from interconnected economic, legal, regulatory, policy and clinical factors. It also described the actions FDA was taking to prevent drug shortages before they occurred, in addition to actions it was taking in response to drug shortages once they had occurred. It further provided recommendations on immediate and longer-term actions to improve FDA's internal processes to prevent and mitigate shortages. Activities working with manufacturers to prevent and mitigate shortages by each of the FDA's divisions were elaborated upon in the report.

The impact of early notification to FDA of a potential supply disruption was noted to be key as stated by FDA Commissioner Dr Margaret Hamburg in May 2012:

> "*Early notification to FDA of potential disruptions in drug supply has made a huge difference in our efforts – and the numbers really tell the story. Since reaching out to industry, there has been a <u>six-fold increase in early notifications</u> from manufacturers. Also, in that six-month timeframe, we have been able to prevent 128 drug shortages, and we're seeing fewer numbers of shortages occur – 42 new drugs in shortage reported in 2012, compared to 90 new shortages at this time last year."* (Mulcahy, 2012)

Title X of the Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted in July 2012 to address the issue of drug shortages (FDASIA, 2012), emphasising the high priority that FDA was placing on resolving the drug shortage issue. It expanded the FDA's authorities and strengthened its ability to advance and safeguard public health by giving FDA the authority to:

- collect user fees from pharmaceutical companies to fund reviews of innovator drugs, medical devices, generic drugs and biosimilars

- promote innovation to speed patient access to safe and effective products
- increase stakeholder involvement in FDA processes, and
- enhance the safety of the drug supply chain

FDASIA also amended section 506C of the Federal Food, Drug, and Cosmetic Act, requiring manufacturers to notify FDA of a discontinuance or interruption in production of life-saving, life-sustaining drugs, or drugs used in the prevention or treatment of a debilitating disease or condition. FDASIA directed FDA to establish ***a task force on drug shortages*** that would develop and submit a Strategic Plan to FDA to enhance FDA's response to preventing and mitigating drug shortages.

In early 2014, FDA provided an annual report to Congress on drug shortages in the calendar year 2013, describing the seven requirements that helped them prevent 140 shortages in the first three quarters of 2013 (FDA, 2014). One of those requirements related to identifying the number of instances in which FDA had exercised regulatory flexibility and discretion in order to prevent or alleviate a drug shortage. Another requirement related to reporting the number of manufacturers that had submitted a notification to the Secretary under section 506C(a) during the calendar year.

FDA also published its *FDA Drug Shortages Strategic Plan for Preventing and Mitigating Drug Shortages* (FDA, 2013). That plan identified two central goals with specific tasks under each. The first goal was to strengthen FDA's mitigation response to imminent or existing shortages, and the second was to develop and implement long-term shortage prevention strategies by focusing on the root causes of shortages. It identified actions for external stakeholders also, which included exploring incentives to encourage high-quality manufacturing, better use of manufacturing quality data to make purchasing decisions, ensuring redundant manufacturing capacity and capabilities, and minimising gray market activities (i.e., trade of goods by entities unrelated to the original product manufacturer, through distribution channels unintended by the original manufacturer).

5.2.3 WHO Activities

The sixty-ninth World Health Assembly Resolution (WHA69.25) in 2014:

> *"urged member states to develop strategies to forecast, avert or reduce drug shortages",* and *"called upon manufacturers, wholesalers, global, and regional procurement agencies and other relevant stakeholders to contribute to global efforts to address the challenges of medicines and vaccines shortages, including through participation in notification systems."* (WHO, 2016a)

This resulted in the recognition of a need to develop standard definitions of shortages, to help align stakeholders on key terms. It also resulted in specific actions to support Member States in addressing the global challenges of shortages through the development of a notification system, including mechanisms to better detect and understand the causes of shortages. Two draft definitions resulted from working groups, and were reported to the WHO Executive Board as part of the progress on WHA69.25 – one definition focused on the supply aspects and the other on the demand aspects of the overall supply chain as follows:

> *"On the supply side:*
> *A "shortage" occurs when the supply of medicines, health products and vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs. This definition refers only to products that have already been approved and marketed, in order to avoid conflicts with research and development agendas.*
>
> *On the demand side:*
> *A "shortage" will occur when demand exceeds supply at any point in the supply chain and may ultimately create a "stockout" at the point of appropriate service delivery to the patient if the cause of the shortage cannot be resolved in a timely manner relative to the clinical needs of the patient."*(WHO, 2016d)

Even though it was agreed that the draft definitions would be used by the WHO secretariat for work going forward, it was acknowledged that adapting to and implementing the definitions would be challenging since the context across various shortages is often complex – another recognition of shortages being a 'wicked problem' as described in Chapter Four of this thesis.

It is important to note that, thus far, based on a detailed review of the activities initiated by EMA, FDA or WHO, the researcher found that none of them focused on understanding and addressing the impact of ***slow continual improvement and innovation*** in the pharmaceutical industry in the context of drug shortages.

5.3 Industry's Response to Drug Shortages: Researcher's Involvement

Most pharmaceutical companies have been challenged with addressing the growing problem of drug shortages, causes of which have become increasingly complex over the past 10 years. Most shortages are addressed by the companies and regulators from each impacted country, on a case-by-case basis, and often this is not until a product is already in an impending shortage situation. With the increased concern and focus from regulatory authorities such as FDA and EMA, and the requirement and expectations of early notifications of shortages to the relevant regulatory authorities, pharmaceutical companies started to focus their attention on ways to systematically reduce shortages. One of the challenges companies faced is that there were no consistent processes or communication mechanisms to regulatory authorities in place that met the expectations of all countries for managing drug shortages. While common discussions across countries started improving the situation through the focused efforts of WHO and EMA, a position of global harmonisation in this area was not achieved and is still far from realisation.

The researcher has been involved in various PQS and QRM related topics since 2003, details of which are described in Appendix I. In particular PDA provided the researcher with a mechanism to connect with the pharmaceutical industry and regulators to bring them together to advance the interactions, dialogue and practical applications of ICH Q8, Q9, Q10, Q11 and Q12. With the heightened global focus on reducing drug shortages, starting in 2012, the researcher was also instrumental in forming and leading a PDA Drug Shortage Task Force for the development of PDA Technical Report 68, as stated in Chapter Two, section 2.2 of this thesis; in this leadership role, she also represented PDA on the EMA's Inter-Association Task Force, formed in 2013, details of which are provided in section 5.3.3 and 5.3.4. In addition to the finalised model published in PDA's Technical Report 68, the researcher also developed templates, tools and training material designed to support the implementation and use of the model by pharmaceutical companies.

5.3.1 Interactions with European Medicines Agency (EMA)

This section describes the researcher's interactions and involvement with the EMA and the work carried out by the researcher as part of the EMA-sanctioned Drug Shortages Inter-Association Task Force, as co-lead and PDA's representative on the activities scoped within the Task Force's charter.

As noted earlier, in 2012, the EMA published a *Reflection Paper on Medicinal Product Supply Shortages caused by Manufacturing/Good Manufacturing Practice Compliance Problems* (EMA, 2012) and an associated implementation plan (EMA, 2015b). These were intended to raise public awareness of the challenges with drug shortages and to implement short and mid-term actions over 3 years. Per one of the short-term actions in this Reflection Paper, in October 2013, EMA organised a public workshop with stakeholders (EMA and NCAs, pharmaceutical industry, patient and healthcare representatives) at their London EMA headquarters. The researcher participated in the workshop representing PDA as the lead for PDA's Drug Shortage Task Force. At that workshop, EMA requested the pharmaceutical industry via various pharmaceutical industry associations to provide an integrated action plan with solutions for managing drug shortages caused by manufacturing, quality and/or GMP compliance issues. They additionally requested the pharmaceutical industry associations to propose ways to improve communications related to supply issues to authorities.

A Drug Shortage Inter-Association Task Force was sanctioned by EMA in November 2013 to address this call from EMA. Membership of the Task Force included the pharmaceutical industry associations that represented a broad section of innovator, generic & biosimilar, plasma protein pharmaceutical and biopharmaceutical companies - PDA, International Society for Pharmaceutical Engineering (ISPE), European Federation of Pharmaceutical Industries and Associations (EFPIA), European Generic and Biosimilar Medicines Association (EGA), Plasma Protein Therapeutics Association (PPTA) and AESGP (Association of the European Self-Medication Industry). The researcher with Vinther represented PDA on this EMA sanctioned Inter-Association Task Force, co-leading the deliverable on risk-based drug shortage prevention at the

product level. The work from this Task Force including the researcher-led deliverable is described in sections 5.3.3 and 5.3.4.

5.3.2 Researcher-Led PDA's Activities on Drug Shortages

As part of the pre-research foundational work, described in Appendix I, the researcher led a PDA Commenting Team that provided feedback to FDA in March 2013 on its FDA Drug Shortages Strategic Plan (FDA, 2013). In June 2013, the researcher via a PDA meeting with FDA on the topic of drug shortages, shared progress on the development of PDA Technical Report 68 and the risk-based concept and model being developed by the researcher for the prevention and management of drug shortages was presented. The researcher and her PDA colleagues also informed FDA of PDA's plan to hold a workshop on Drug Shortages in September 2014 that would be chaired by the researcher. The FDA supported the development of such a risk-based approach, the use of a workshop to get input on it, and it indicated that it looked forward to seeing the risk-based framework published and implemented by pharmaceutical companies.

The researcher presented on risk-based application specifically for the management of drug shortages at the September 2013 PDA/FDA Joint Regulatory Conference, and this helped raise awareness of the growing global challenges with drug shortages and initiated an ongoing dialogue within the pharmaceutical industry on the proactive role that pharmaceutical companies must play to prevent drug shortages. In that presentation the initial thinking on a structured application of QRM and KM concepts to address the problem of drug shortages was presented. In addition, the researcher presented an early draft of the risk-based triage approach focused at the product level, which the PDA Drug Shortage Task Force, led by the researcher had started developing in 2012. As discussed in section 5.3.4, the Risk Triage model eventually became the solution delivered to EMA via its Drug Shortage Inter-Association Task Force.

Throughout 2013-2014, the researcher continued to raise awareness of the need to apply QRM and KM principles and concepts to the problem of drug shortages; she continued to socialise and encourage dialogue between stakeholders and regulators, while at the same time working on the development of the Risk Triage model. This comprised of

presentations and discussions led by the researcher at PDA's Annual Conference in 2014, the PDA QRM Interest Group, Drug Shortage workshops, and publications (all of which are noted in Appendix I). The researcher used all these channels to gather input and refine the Risk Triage model for publication in Technical Report 68.

PDA Drug Shortage Workshop

Specifically, the 10-11-September-2014 ***PDA Drug Shortage Workshop*** held in Washington DC, was chaired by the researcher. This workshop brought together the pharmaceutical industry and regulatory authority participants, including global regulatory senior personnel from FDA and EMA, along with senior leaders from global pharmaceutical companies and pharmaceutical industry associations, who shared their insights, experiences and lessons learned. The objectives of the workshop were to explore:

- the application of risk and knowledge management in the prevention of, and response to, drug shortages
- incentives for manufacturers to build in proactive end-to-end controls and good practices in their manufacturing processes and supply chains such as:
    - redundant capacity and new technology
    - more transparency and linkages to supply planning
    - manufacturing site metrics and quality standards for potential manufacturing partners, purchasers and prescribers
    - focusing on root causes and solutions related to manufacturing, product quality and supply continuity

Highlights of the workshop are given below:

Capt. Valerie Jensen (FDA), who led the Drug Shortages Team at FDA (CDER), presented progress on FDA's strategic plan for drug shortages, reviewing drug shortages statistics and offering FDA's perspective on the causes of drug shortages. These included the lack of manufacturing redundancy and flexibility, complexity in manufacturing processes, and the lack of technology improvements and innovation. Jensen described specific tactics FDA used to prevent and mitigate shortages, such as using regulatory discretion to allow manufacturers with low-risk quality issues to

continue production of medically necessary drugs, or requesting other companies to ramp up production. In particular Jensen reported that:

> *'Some shortages have been ongoing for a long period; FDA encourages companies to submit applications for these products.'*

Dr Sabine Haubenreisser (EMA), EMA's liaison at FDA, presented the European perspective, highlighting the complexity of the drug shortages issue and the need for multi-disciplinary teams to resolve it. According to Haubenreisser, most drug shortages in Europe fell under the remit of national authorities, with EMA getting involved in shortages for CAPs or when coordination across national agencies was needed. EMA's actions included consultation with its scientific committees, discussions with heads of national medicines agencies, and a Call to Action public workshop with stakeholders (13-October-2013), as discussed in section 5.2.1. She encouraged the pharmaceutical industry to perform proactive risk management and to improve communications with regulatory authorities; she encouraged pharmaceutical industry associations to continue their work on developing and sharing methodologies for the assessment, communication and mitigation of drug shortages.

In addition to the regulatory presentations, the workshop featured presentations of work-in-progress by different pharmaceutical industry associations (EFPIA, ISPE, PDA), in particular their work on the possible root causes of shortages, of which two were highlighted: **aging facilities or equipmen**t, as presented by **Maik Jornitz** (G-Con) and **regulatory hurdles for PAC management**, as presented by **Anders Vinther** (Sanofi). Finally, two generic product companies, represented by **Share Ernst** (Hospira) and **Andreas Brutsche** (Sandoz), illustrated how they addressed and mitigated drug shortages within their own companies. Hospira, which had a long history with drug shortages, shared that they had implemented a proactive approach to resolving and preventing drug shortages, forming strong partnerships with government agencies and pharmaceutical groups, and taking a risk-based approach to managing their supply chains and strengthening their manufacturing operations network. After facing drug shortage issues, Sandoz took a three-tiered approach to remediation which included business continuity planning, rigorous governance processes, and a cultural change in mindset and behaviours to achieve a sustainable quality culture.

In addition, the workshop included multiple breakouts on manufacturing risk identification and mitigation, supply chain risk identification and mitigation, barriers and incentives for new technologies and innovation to mitigate risks of drug shortages in aging facilities. The breakout sessions and panel discussions generated extensive dialogue on potential solutions, and these formed a part of the researcher's continued development of the risk-based triage model and exploration into how slow PAC processes led to inadequate continual improvement, innovation, thus contributing to potential drug shortages.

5.3.3 EMA Drug Shortages Inter-Association Task Force

The rest of this chapter focuses on the work of the EMA Drug Shortages Inter-Association Task Force, established in November 2013. While each pharmaceutical industry association that participated in the Task Force already had several ongoing activities, the joint Drug Shortages Inter-Association Task Force served to coordinate the unique perspectives and solutions from all of the associations involved. The organisations focused on the scientific and technical elements of restrictions in supply due to quality and manufacturing issues including root causes, risks, prevention and control throughout the supply chain that fell within the scope of responsibilities of a manufacturer and/or MAH. Economic and business-related root causes and supply interruptions by other players in the supply chain though also likely causal factors, were out of scope of this team's deliverables.

The Task Force took a three-phased approach, as follows, for their work:

- **Phase 1:** Each association would finalise their deliverables according to their individual milestones and timelines.
- **Phase 2:** The joint team would develop a plan to be presented to EMA before the end of January 2014 that would include a series of proposals based on results from the existing activities (Phase 1). It would also recommend new activities which were considered worthy of further evaluation against the goal of reducing drug shortages caused by manufacturing and/or quality issues.
- **Phase 3:** EMA would review the proposals and determine which of the proposals they would support and be further engaged in advancing. The

associations, through the joint team, would share plans and collaborate as relevant to ensure that significant areas of drug shortages were covered. During Phase 3 the associations would also deliver conference sessions, meetings, workshops, etc. with interested parties and publications detailing progress and requesting feedback.

The goal for the joint team was, by October 2014, it would deliver to EMA a series of reports (white papers, best practices), presentations, training materials, etc., that could assist both pharmaceutical companies and regulators in addressing drug shortages. The next part of this chapter focuses on the deliverables for each of the associations as part of the Inter-Association Task Force's charter, which were performed complementarily and collaboratively under two workstreams, as follows:

1. The first workstream involved the individual member-based associations of PDA and ISPE, who were chartered to deliver a proposal and a plan to EMA to address the prevention of drug shortages due to manufacturing and quality issues. The researcher co-led the PDA team that was a part of this Drug Shortage Inter-Association Task Force.
2. The second workstream under the remit of the pharmaceutical industry trade associations EFPIA, EGA, PPTA, and AESGP, was chartered to address communication principles and a reporting framework between the MAH and regulatory authorities.

The complementary solutions developed by the various pharmaceutical industry associations were intended to:

- enable a shift from reactive to proactive prevention of shortages at a root cause-based system level (ISPE) and a risk-based prevention plan at a product level (PDA)
- address harmonised communication principles to regulatory authorities for manufacturing and quality issues-driven supply disruptions (EFPIA, EGA, PPTA, AESGP)

A summary of the solutions developed and the recommendations from the Inter-association Task Force was published in a report that was provided to EMA in December 2014 (EMA Drug Shortages Inter-Association Task Force, 2014a).

ISPE developed a holistic system-based *Drug Shortages Prevention Plan (DSPP)* that described a framework based on six dimensions – corporate quality culture, robust quality system, metrics, business continuity planning, communication with authorities and building capability (ISPE, 2014). The intent was for companies to use the DSPP at a system level to look holistically across their entire supply chain and identify potential gaps and an appropriate action plan.

EFPIA, EGA, AESGP and PPTA developed *Quality and Manufacturing Driven Supply Disruptions: Industry Communication Principles to Authorities* (EMA Drug Shortages Inter-Association Task Force, 2014b) to enable transparency and predictability in the management of drug shortages by:

1. Harmonising definition of a meaningful disruption to supply
2. Harmonising reporting content with initial categorisation based on PDA's Risk Triage model (described in PDA Technical Report No. 68)
3. Harmonising timepoint and recipient of the information at NCAs and EMA

PDA's response to the EMA Inter-Association Task Force revolved around the work carried out by the researcher for the development of Technical Report 68. The next section of this chapter will take a deeper look into this.

5.3.4 PDA Technical Report 68: Risk-Based Approach for Prevention and Management of Drug Shortages

PDA's deliverable as part of the EMA Inter-Association Task Force was Technical Report No. 68. It provided an easy step-by-step guide to proactively identify and manage drug shortage risks caused by manufacturing and quality issues in the end-to-end product value chain. The PDA Technical Report provided a practical structured approach consisting of:

1. A holistic risk-based framework at a product level for the prevention and management of drug shortages caused by manufacturing and quality issues.
2. A Risk Triage model that could be used to assess drug shortage risks and implement appropriate controls in the end-to-end value chain for manufacturing and distribution of a product.

3. Templates for developing a Drug Shortage Risk Register and a Drug Shortage Prevention and Response Plan at a product level, especially for products classified as being at risk level A (based on their therapeutic use and the availability of alternative treatments).

The framework provided in the report also supports and enables MAHs to meet the requirements of Section 506C of the Federal Food, Drug and Cosmetic Act and Article 13 of the EU GMP Directive 2003/94/EC, which obliges them to notify relevant regulatory authorities in a timely manner in the event of a meaningful disruption or potential drug shortage.

PDA Technical Report 68 also described management responsibilities and expectations related to prevention, management and notification of drug shortages to regulatory authorities. In addition, it provided ways for pharmaceutical companies to engage more proactively with regulatory authorities through use of PAC management plans and harmonised global change protocols, to expedite the review and approval of PACs by multiple regulatory authorities. The report claimed that such protocols could also be helpful for companies to address the risk of drug shortages due to aging facilities, processes and analytical technologies by modernising their facilities and implementing new technologies (equipment, processes, and analytics).

As the risk to patients from a potential drug shortage increases, the level of rigor, effort, and cross-functional collaboration within an organisation to address the risk should also increase. This effort should be coupled with effective and timely communication between the MAH and regulatory authorities to proactively manage drug shortage risks. The Technical Report leveraged the guidance developed by EFPIA, EGA, AESPG and PPTA for communications between MAHs and regulatory authorities.

A high-level overview of this risk-based approach for the prevention and management of drug shortages was first published in April 2014 in a PDA Letter article (Ramnarine, Roenninger and Vinther, 2014). This also served as a means for the researcher to socialise and invite feedback on the risk-based approach from the broader pharmaceutical industry community.

The holistic Risk Triage model developed by the researcher at a product level for prevention and management of drug shortages caused by manufacturing and quality issues, included a step-wise assessment approach that started with product categorisation, identification and assessment of drug shortage risks, development of a Drug Shortage Risk Register, and finally a Drug Shortage Prevention and Response Plan:

- Categorising each product by criticality based on its indication and patient needs
- Establishing a Drug Shortage Risk Register (a single source of information on risks that can result in drug shortages) by proactively identifying and assessing risks (to quality, compliance, and supply) that could lead to a shortage
- Ensuring timely reduction and management of risks by completing risk control actions defined in the risk control plan, based on criticality
- Establishing a Drug Shortage Prevention and Response Plan, with a particular focus on medically necessary, life-supporting or life-sustaining products. Communication of these plans with regulatory authorities would improve response and recovery times from a shortage, when one did occur

The Risk Triage model and the Drug Shortage Prevention and Response Plan is applied at a product level and is depicted in Figures 5.1 and 5.2; both are described in detail in PDA Technical Report 68.

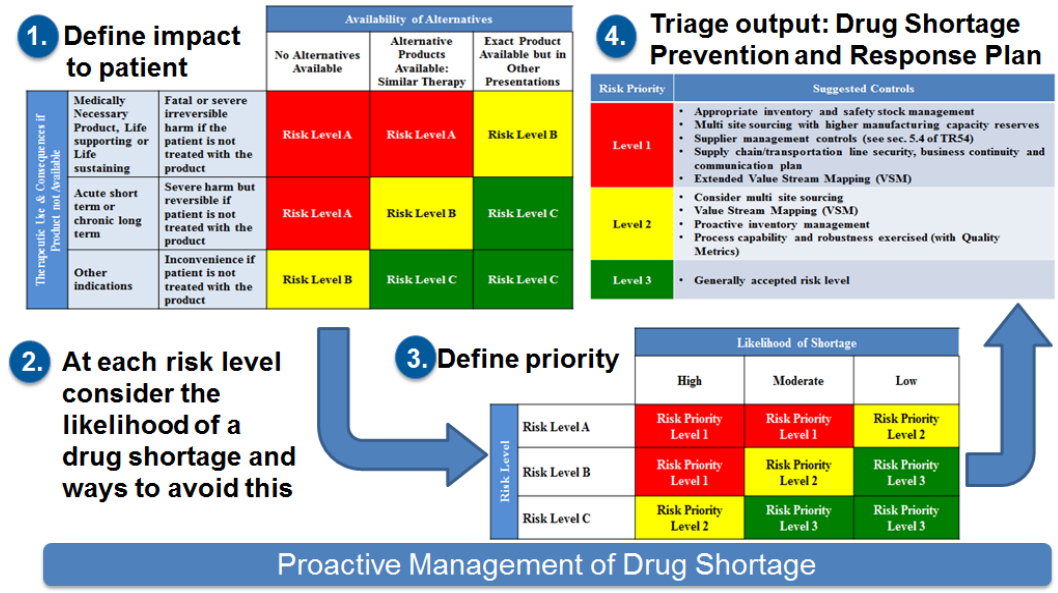

Figure 5.1: Risk Triage Model: Categorisation, Patient Impact and End-to-End Controls (Ramnarine *et al.*, 2014)

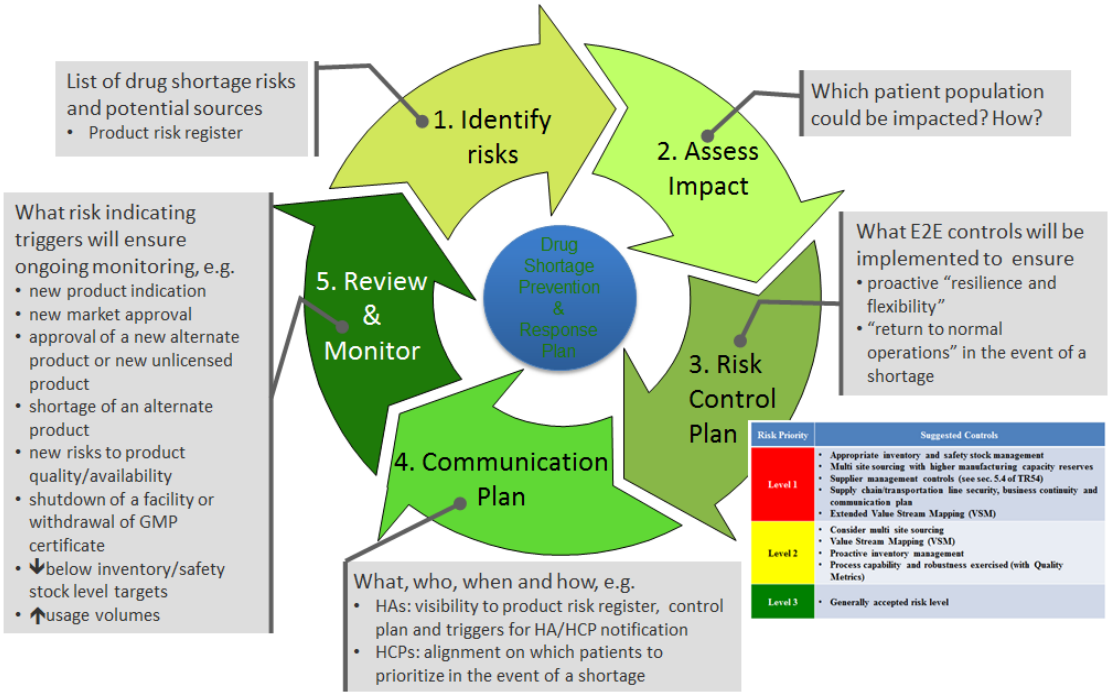

Figure 5.2: Drug Shortage Prevention and Response Plan for a Product (Ramnarine *et al.*, 2014)

<u>Use and Benefits of the Product Level Risk-Based Prevention Triage Model</u>

The Risk Triage model is a practical risk-based application targeted to be used in the case of drug shortages caused by manufacturing and quality issues. There is evidence

that it, as well as PDA Technical Report 68 in general, has been viewed as an important part of the solution to drug shortages. For example, EMA and several NCAs have actively advocated its use by both pharmaceutical companies and regulatory authorities. In July 2019, EMA issued a *Guidance on Detection and Notification of Shortages of Medicinal Products for Marketing Authorisation Holders (MAHs) in the Union (EEA)* (EMA, 2019); this advised MAHs to utilise PDA's Technical Report 68. It has also been cited by EMA in its public presentations on medicines shortages (Houÿez, 2015).

In 2021, the Expert Working Group assigned to the revision of ICH Q9, *Quality Risk Management*, communicated to the PDA the value that the Technical Report 68 presented to its work on product availability risks, and it requested a copy of the report for the EWG to use, as it developed new guidance in relation to the management of such risks. The ICH Q9(R1) Rapporteur for the revision work confirmed to the researcher in 2021 that the EWG also intended to make use of the Technical Report when training materials were developed in the latter half of 2021 and in early 2022 to support the revisions made to the guideline. He indicated that the value of the Technical Report was also one reason why the EWG had identified the PDA as a key, non-ICH member stakeholder that would be invited in mid-2021 to send suggested case studies and other training materials to the EWG for consideration by the EWG in relation to product availability risks and other QRM-related topics. That invitation was communicated to the researcher and to the President of the PDA by the ICH Q9(R1) Rapporteur on 6-August-2021.

Use and Benefits for Regulators (including Inspectors): PDA Technical Report 68 can be used by regulators to enable the following:

- A shift from reactive to proactive management of drug shortage risks in alignment with the principles of ICH Q9, *Quality Risk Management* and ICH Q10, *Pharmaceutical Quality System*
- Ensure that the QRM policy and procedures at companies make provision for the proactive management of product availability (drug shortage) risks
- Raise awareness and reinforce the application of the risk-based concepts, tools and templates at a product level

- Bring attention to the importance of training activities and the need for training resources, especially for companies that are in more of a reactive state related to the management of shortage risks
- Leverage relevant elements of the Drug Shortage Risk Register (especially for medically necessary, life-saving or life-supporting products) to engage in proactive dialogue and partnership with companies on management of drug shortage risks

Use and Benefits for Pharmaceutical Industry: Companies should have robust QRM and KM systems to both prevent (proactive) and respond (reactive) to drug shortages. Practical application by a pharmaceutical company of the risk-based triage model at a product level, including the Risk Triage tool and its templates, will allow companies to be more proactive in identifying potential drug shortage risks in their manufacturing and supply chain operations. Being proactive will enable better control of identified risks, the prevention of shortages, and the ability to respond and quickly recover in the event of a shortage. The Drug Shortage Prevention and Response Plan also offered a mechanism to share potential shortage information proactively with regulatory authorities and collaborate with them in developing a suitable communication and response plan in the event of a drug shortage.

5.3.5 EMA's Response to the Drug Shortages Inter-Association Task Force Solutions

EMA, EU NCAs and FDA have been supportive and have encouraged use of the solutions developed by the Inter-association Task Force; EMA advised MAHs to utilise the PDA and ISPE solutions in their shortages guidance issued in 2019 (EMA, 2019). PDA Technical Report 68, the Risk Triage tool, and templates for Drug Shortage Risk Register and Drug Shortage Prevention and Response Plan, were made available for free and can be downloaded by anyone for use at www.pda.org/drugshortage. The Technical Report and its templates facilitate and encourage companies to engage in a more proactive dialogue with regulatory authorities on this topic.

Progress on the Drug Shortages Inter-Association Task Force's work was presented by the representatives from each of the associations, to EMA and the EU Inspectors

Working Party at periodic intervals. The researcher presented for PDA. Upon completion of the set of solutions by the Associations, a final report was prepared and submitted to the EMA (EMA Drug Shortages Inter-Association Task Force, 2014a). The EMA received all the solutions very positively, as evidenced by EMA referencing them in its 2019 guidance (EMA, 2019) on medicines shortage; EMA acknowledged that the combined body of work was very informative, and that it would integrate them into its next steps of continued work on the topic of drug shortages. EMA also agreed to make the solutions available on the EMA website with recommendations that NCAs post them online as well.

The PDA Risk Triage model was recommended by EMA for implementation by MAHs and use by NCAs for the proactive identification and management of shortages, and the timely communication and collaboration with regulatory authorities.

Additional dialogue has continued within the European Commission, EMA and EU Member States on further actions to address this problem of drug shortages. Awareness of the global complexity for PACs, its impact on continual improvement and innovation, and its connection with drug shortages, has gradually started entering the dialogue since 2020. Though these discussions are still in their infancy, as expected, this research study has served to increase awareness and has activated a better understanding of the challenges presented by slow PAC timelines.

From this point forward, the thesis focuses on addressing transformation of PAC management through science and risk-based approaches within the framework of an effective PQS.

Part Three: Exploring and Contributing to Regulatory Authorities' Positions in Context of the Research

Part Three explores the regulatory landscape and the vision and position of key regulatory authorities on the global problem laid out in Part Two. Regulatory Authorities are one of the primary stakeholders in relation to this problem and for the design and implementation of solutions. Therefore, this part of the research study was essential in exploring and determining key aspects that must be addressed from the perspective of regulatory authorities.

Chapter Six

Exploring and Contributing to Regulatory Authorities' Positions

In parallel with the activities around bringing the pharmaceutical industry together, as described later in Part Four, the researcher sought opportunities to solicit the opinions of one of the other key stakeholder groups in the drug shortage crisis, those of the regulators. Improved public health requires reliable availability of quality drugs. Continual improvement requires the continued implementation of new knowledge and it is essential for achieving product realisation and maintaining a state of control. Continual improvement is desired and expected, yet it can take years to implement new knowledge in daily operations in a large part due to the global regulatory complexity.

The activities from this point forward in the research were initiated at the request of the FDA - to unify the pharmaceutical industry and bring its senior Quality leaders together on the topic of PAC management and accelerating continual improvement and innovation in the pharmaceutical industry. This required the researcher to also further explore the position of other regulatory authorities, given the challenges with drug shortages and the fact that continual improvement and innovation are global issues and not confined only to the US.

This chapter describes the exploration activities conducted by the researcher with regard to regulatory authorities, starting with the FDA and then the Pharmaceutical Inspection Cooperation Scheme (PIC/S), the European Commission (EC), WHO, and the International Coalition of Medicines Regulatory Agencies (ICMRA). The chapter also lays out the aspects where the researcher specifically provided input into, and influenced the development of, certain regulatory authority positions, strategies and guidances.

6.1 US Food and Drug Administration

This section describes the activities conducted by the researcher with the FDA within the context of the FDA's 21st Century Initiative and its components that were relevant for the topic of this research.

6.1.1 Context of FDA's 21st Century Initiative

In 2004, the FDA published its final report on pharmaceutical quality for the 21st century (FDA, 2004), which laid out a vision to modernise pharmaceutical manufacturing and enhance product quality.

The FDA's vision for the 21st century was launched before ICH Q8, ICH Q9 or ICH Q10 were published. The development of ICH Q8 and ICH Q9 had only just begun and the report stated FDA's interest to actively participate in the development of those guidances. Dr Woodcock, Head of CDER at the FDA, stated that the realisation of this 21st century vision would result in:

> *"a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."* (FDA, 2004)

The objectives of this 21st Century Initiative by the FDA included the following:

- *"Encourage the early adoption of new technological advances by the pharmaceutical industry*
- *Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance*
- *Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas*
- *Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science*
- *Enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities."* (FDA, 2004)

With a key public health focus, this initiative by FDA was intended to shift the current CMC review assessment system from a compliance-based approach to a new risk-based pharmaceutical quality assessment system, in order to provide a scientific framework that would enable mitigation of risks while facilitating continuous improvement and innovation in pharmaceutical manufacturing. This new assessment system was expected

to reduce the regulatory burden and enable manufacturers to improve their efforts towards continuous improvement and process optimisation. These progressive science and risk-based expectations from FDA laid out prior to the ICH Q8, 9, 10 made their way into these ICH guidances a few years later. Regardless the shift from a compliance-based to more science and risk-based assessments that enable technological advancement, state-of-the-art pharmaceutical science, and application of modern QMS concepts, has been discouragingly slow. Pharmaceutical companies have advanced implementation of the ICH Q10 PQS model, yet comparable progress in the *integration of enhanced quality systems approaches into regulatory authorities' processes and policies for reviews and inspections* as envisioned by FDA, has not been made.

The report also articulated FDA's intent to increase its collaboration with international health and regulatory partners through multilateral and international forums such as ICH and PIC/S, in order to harmonise pharmaceutical quality standards and requirements as much as possible. FDA has indeed driven several activities in this regard, an example being the latest ICMRA strategic initiative on PQKMS, described in section 6.5 (ICMRA, 2021).

In regards to risk-based regulatory oversight, the report stated that the intensity of FDA oversight should be based on the degree of a manufacturer's product and process understanding and the robustness of the quality system controlling its processes, among other factors, such as criticality to product safety and public health. This implied that complex or less understood processes (from a manufacturing or quality attribute perspective) might require higher regulatory oversight, whilst process changes for well-defined and well-understood processes could be managed under a company's change control procedures. This eventually became a part of ICH Q10 Annex 1. Though the report discussed risk-based approaches within a quality system framework, it did not provide details of how a risk-based change management system might work. Regardless, the risk-based approach that was suggested was intended to reduce the frequency and/or scope of inspections, by focusing inspections on areas that had highest public health impact. FDA's hope was that these science and risk-based regulatory oversight approaches would provide positive incentives for pharmaceutical companies to implement effective quality systems, and that they would result in facilitating

continual improvement in manufacturing along with improving the availability of medicines for patients, while increasing product quality and process efficiency.

In regards to FDA's science-based policies and standards to facilitate continuous improvements, the report described the use of comparability protocols. In 2003, FDA established a *'Changes Without Prior Review Working Group'* to identify options for performing a systematic risk-based review of post-approval manufacturing changes, and to establish a mechanism for regulatory relief through the use of comparability protocols. A comparability protocol predefined a comprehensive change evaluation plan that included specific tests and studies, analytical procedures, and acceptance criteria in order to demonstrate that there was no adverse effect of a CMC PAC on the safety or effectiveness of the drug product. The use of a comparability protocol could allow an applicant to implement a CMC change without waiting for prior-approval from FDA, and, therefore, to allow distribution of a product sooner than would be possible without the use of such a protocol. It was also envisaged that a comparability protocol would provide a means to facilitate process improvements and/or process optimisation which, in some cases, could even prevent and/or mitigate a supply disruption or shortage situation.

6.1.2 Exploring FDA's Position

The researcher believed that the vision and expectation that FDA had communicated in 2004 through their 21st Century Initiative, even prior to ICH Q8, Q9 and Q10 being published, was a step in the right direction. Yet, forward progress in delivering against the vision and objectives of that initiative had been very slow; the pharmaceutical industry and its regulators were still a long way from achieving the value for patients as envisaged by the 21st Century Initiative by the time this PhD research commenced, despite the strong intent and commitment of all stakeholders. This was evidenced by the fact that innovation and continual improvements still were taking years to implement in many cases even after the availability of tools such as comparability protocols.

The researcher established the PDA PAC iAM[SM] Task Force, which recognised that the pharmaceutical industry had a more active role to play if realisation of FDA's 21st Century Initiative was to occur, and if the concepts and objectives of ICH Q8, Q9 and

Q10 were to be realised at a practical level. Thus, the researcher led the Task Force through several conferences and workshop discussion sessions, which involved colleagues from various pharmaceutical companies as well as regulators. For example, in August 2018, the Task Force invited representatives from 13 global companies for a workshop hosted at the PDA Headquarters in Bethesda, to explore what pharmaceutical companies could do to contribute towards solving the problem of global PAC management complexity that was stifling innovation.

A significant outcome of that workshop was the agreement of its participants that Senior Quality Leaders within the pharmaceutical industry could (and should) speak with one voice, to create an industry-wide common approach to comprehensive PAC management. It was agreed that the Quality Leaders could:

- Emphasize the role of QRM for PACs
- Agree on a common understanding of what is meant by 'an effective PQS for PACs', since there has been no guidance, clarity or alignment across the industry and/or regulatory authorities on what an effective PQS is and how it might be demonstrated
- Drive the implementation of this 'effective PQS for PACs' within their respective companies
- Raise awareness about the role that reduced regulatory burden could play in achieving the objective of uninterrupted availability of high-quality medicines for patients

It was acknowledged that, while companies' representatives can participate in active dialogue about PACs, they generally did not have control or authority over deciding regulatory outcomes for individual PACs, for creating mutual reliance among regulators, or for reducing the level of global regulatory complexity that was associated with many PACs. This complexity is described in Figure 6.1, which was developed by the researcher and Vinther; it illustrates that while companies have a direct role to play along the ***Science*** axis, they cannot influence the ***Reliance*** axis, which in this context means that, if one regulatory authority has assessed a PAC or a company's PQS, other regulatory authorities could place reliance on and accept that regulatory authority's conclusions (of acceptance or rejection about the PAC or the PQS). Companies cannot

of course influence how much mutual reliance is in place between regulatory authorities – and this is as it should be. Even along the ***Science*** axis, after companies complete a science and risk-based assessment of a PAC, regulatory authorities still have the final decision on whether or not a prior-approval submission is needed. Therefore, making a meaningful difference will require both the pharmaceutical industry and regulatory authorities to work together and advance both axes, so that the global complexity associated with PACs could be overcome to a significant extent. This became an important component of the activities undertaken by the *1VQ for PAC Initiative* and is described in Chapter Seven and Chapter Eight of this thesis.

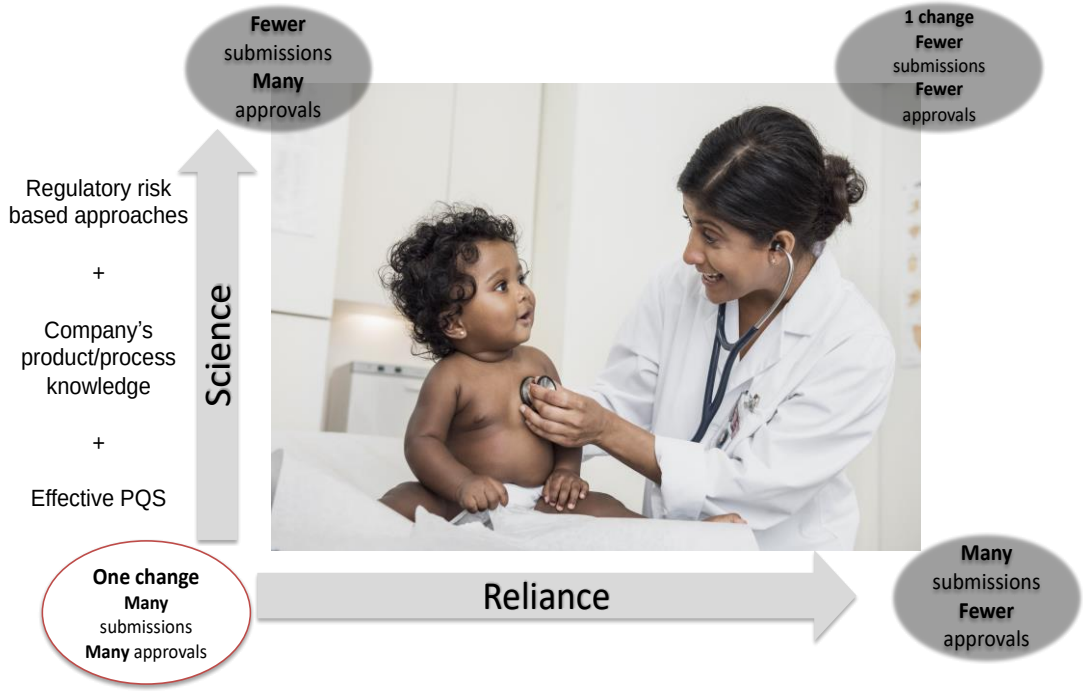

Figure 6.1: Pharmaceutical Industry and Regulatory Authorities Working Together

Prior to August 2018, the focus of ICH Q12 development was mainly on regulatory CMC aspects. Little attention was given to the practical realities of quality operations during the commercial phase of a medicinal product, where a lack of continual improvement and innovation created significant challenges, or to the role an effective PQS could play in reducing the number of PACs that need regulatory prior-approval. To address this, at the workshop in August 2018, the pharmaceutical industry came together to speak with one voice – and a ***One-Voice-of-Quality (1VQ) for PAC***

Initiative was born. This initiative had the researcher as its co-lead, and it had the purpose of putting a strong focus on the importance of implementing new knowledge to continually improve and innovate faster and contribute to reducing drug shortages. From the very beginning, the *1VQ for PAC Initiative* decided not to focus on the Reliance axis or what regulatory authorities could do; it instead focused on what the pharmaceutical industry could do to drive better science and risk-based decision-making for PACs and ensure an effective PQS within their companies. A second *1VQ for PAC* workshop was held in November 2018, also hosted at the PDA Headquarters in Bethesda. At it, the *1VQ for PAC Initiative* planned to develop practical solutions to address PAC complexity, by standardising the approach to PAC management across the pharmaceutical industry. Details of all the focus group sessions conducted under the *1VQ for PAC Initiative* are discussed in Chapter Seven, section 7.3 of this thesis.

One of the topics mooted at the *1VQ for PAC* focus group sessions was initiating a proactive discussion with FDA to get the regulators' input into the *1VQ for PAC* activities. In order to do this, after the November 2018 session, the researcher and Vinther reached out to Dr Janet Woodcock (Head of CDER at FDA), requesting a meeting with her to discuss PAC management. In January 2019, at the CDER office in Bethesda, senior FDA leaders including Dr Woodcock, accompanied by Dr Ashley Boam (Rapporteur for the ICH Q12 EWG) and other senior FDA leaders, met with the researcher and Vinther. The objective of the meeting was to explore FDA's interest and position on the topic of this research - the 'wicked problem' of the lack of continual improvement and innovation leading to drug shortages in a global environment.

Highlights from the August 2018 and November 2018 *1VQ for PAC* workshops with the 15+ global pharmaceutical companies were presented to Dr Woodcock and her FDA colleagues in January 2019. The need and the decision to establish a one-voice-of-quality within the pharmaceutical industry in solving this challenge was emphasized. The FDA concurred stating that, in order for FDA to enter into productive discussions on this topic, senior leaders in the pharmaceutical industry had to put forward unified positions and standard solutions that could be implemented consistently and that were applied to actual PAC examples. It was also emphasized at the meeting that all attendees at the most recent *1VQ for PAC* workshop had unanimously agreed that the documentation requirements and the level of global complexity that were associated

with PACs and product lifecycle management had increased exponentially over the past decade. It was stated that the current situation was considered to be unsustainable, and this was why the *1VQ for PAC Initiative* had made the decision to take practical actions to improve the handling of PACs, such as through a standardised risk-based approach across the pharmaceutical industry for PAC management, and align on what aspects of the PQS are essential specifically for the effective management of PACs. There was also an agreement at the November 2018 *1VQ for PAC* workshop to align on practical PAC examples that, at that time required prior-approval from regulatory authorities, but which could more reasonably be managed within the company's PQS only, or as a notification to the regulatory authorities, instead of a prior-approval submission.

It is useful to consider the framework of the FDA's 21st Century Initiative that relate to science and risk-based regulatory oversight approaches and tools; these include comparability protocols, ICH Q8's product and process understanding through Quality by Design principles, ICH Q9's systematic QRM framework, and ICH Q10's holistic PQS model. FDA laid out the desired state and the approaches to achieve that state, yet the literature does not indicate or give evidence that the continual implementation of new knowledge that is gained constantly during daily commercial operations has resulted in the extent of continual improvement that was envisaged by the FDA's 21st Century Initiative. It is apparent that these approaches are yet to be fully implemented within the quality and regulatory processes in pharmaceutical companies and regulatory authorities.

PACs only allow filing and implementation of smaller discrete segments of this knowledge, as opposed to the timely implementation of the entire body of relevant knowledge gained from routine operations. Even implementation of these discrete PACs in all countries where the product is marketed can take up to several years, as shown in Figures 1.1 and 1.2 in Chapter One of this thesis. So, the current reality in pharmaceutical manufacturing is far from the state desired in all these well-intentioned initiatives and guidances.

6.1.3 Examples Presented to FDA on Practical Operational Challenges with PAC Complexity

In the January 2019 meeting with senior FDA leaders, the researcher highlighted that every day, operational Quality leaders face the risk of drug shortages and cGMP compliance issues, while not being able to continually improve and innovate in a timely manner due to the extent of global PAC complexity, and the lack of utilisation of science and risk-based approaches when managing PACs. Examples of the enormous PAC logistical complexities that companies live with every day were presented at the meeting, highlighting that the current state in fact introduced risks to a state of control and product availability, which was quite contrary to the desired state for patients. Two of these examples shared are given below:

Example 1

In relation to a pentavalent vaccine manufactured by a pharmaceutical company, 83 batches of the same product (same end product specifications and indication) had been produced using 55 different versions of the manufacturing process within a year. This need to continue to operate so many different versions of a manufacturing process was due to the fact that multiple PACs were under assessment at various regulatory authorities, with varying approval timelines in different countries. This required the company to keep multiple batches in inventory, reflecting the different manufacturing process versions, even though all versions produced an end product that met exactly the same product specifications. This greatly increased the risk of errors, such as the risk of sending a batch manufactured via one process version to a country that hadn't yet approved the PAC for that process, or worse, having the product available in inventory but not being able to supply it to a country as a result of regulatory requirements. This resulted in drug shortages, simply because the PAC for the process that was used to produce that batch had not yet been approved by the regulatory authority of that specific country (even though it had been approved and found acceptable by many other countries).

Example 2

Another example that related to the researcher's direct experience concerned the implementation of a state-of-the-art analytical method with a higher level of sensitivity

than the currently used and approved method. This new analytical method delivered improved testing capabilities, increased innovation, higher speed in product testing and faster batch release decision-making, thus making the product available to patients faster. However, the necessary regulatory approvals for this analytical test method change took almost ten years from the first to last regulatory authority approval. During this period, while submissions of the PAC for approval were being made to each of the relevant countries, the company had to dual test batches of the product, using both the old and new test methods, because the new method had not been approved in all countries. This resulted in an increased dual testing burden and cost on the QC labs, and it introduced compliance risks, such as addressing differences in test results by the two methods, even though equivalency had been demonstrated for both methods. It also presented challenges in determining how to investigate and manage instances where testing by one method met specifications, but where testing with the other method resulted in an out-of-specification result.

It is also noteworthy that, by the time a new technology is finally implemented in all relevant countries, it is highly likely that another technology upgrade has become available in the interim, and the cycle to implement that upgraded technology needs to start all over again, even while the previous 'new' technology is still in the process of being implemented across all countries. This is exactly what happened in the researcher's experience with this particular example, where the company was implementing a new technology - before it had been fully implemented in all countries, an upgrade of the technology was available, and a whole new PAC cycle had to be initiated, even as the previous one was still in progress. The logistical complications that this led to in the testing, release and inventory management of product increased exponentially and it was extremely challenging to manage for QC labs, QA personnel, and supply chain planners.

The question that such real-life examples raised for the researcher was:

> *Given the addition of this enormous complexity with inventory, daily operations management, and long lead-time challenge associated with implementing a new method or technology, why would any company want to invest in taking on this significant effort and the burden of implementing a new technology, improving and innovating, even when it greatly improved the current state, reduced risks and improved product availability for patients?*

It is the researcher's position that the global regulatory complexity for PACs is a significant reason why companies do not have the incentive or motivation to continually improve and innovate; instead, they choose to continue to operate with aging, sub-optimal processes, methods, equipment and technologies that can lead to manufacturing and quality issues and eventually supply challenges. It in fact, works against continual improvement, in contradiction to what all regulatory authorities want and have stated as an expectation in their regulations. The activation energy to overcome the global PAC complexity hurdle is daunting for any company, and even if indirect, it is possible that there is a link between this inertia to improve and drug shortages.

The researcher made the case to the FDA, that a significant shift from years to months (or weeks) was needed in the time it takes from when new knowledge is acquired in daily operations to when it is implemented; this desired shift is depicted in Figure 6.2.

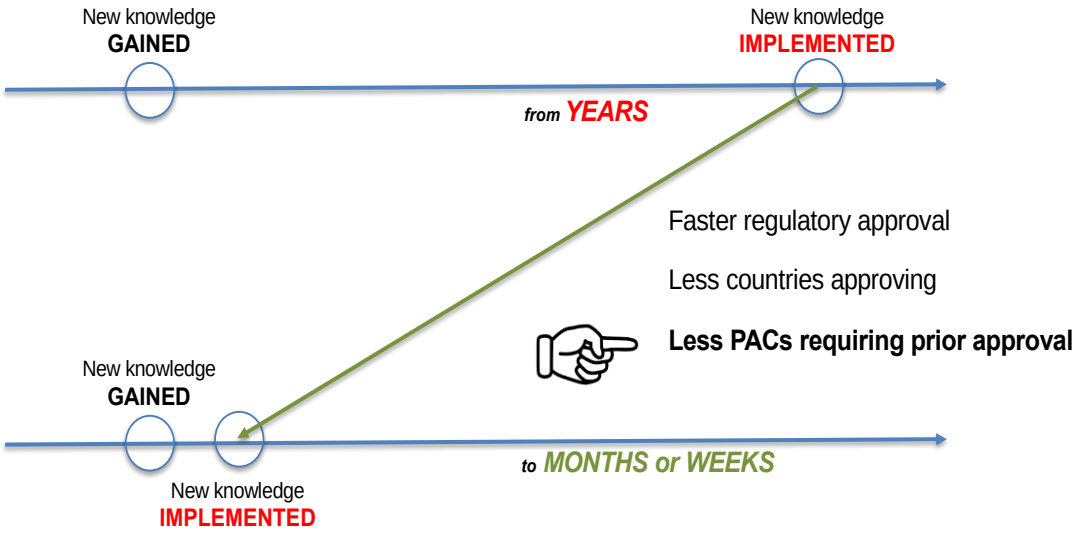

Figure 6.2: A Significant Shift is Needed in Implementation of Improvements Based on New Knowledge Gained

Indeed, these challenges were also in the minds of FDA, where as noted in *FDA Pharmaceutical Quality Oversight: One Quality Voice*:

> *"the number of post-approval supplements received for review has increased over the past decade, in part owing to our current practice of "locking in" an applicant's manufacturing process before it is fully optimized. A burdensome regulatory framework requires manufacturers to submit supplements as they strive for process optimization."* (FDA, 2015)

In this context, it is also noteworthy that new knowledge is gained mostly during the commercial phase as the number of batches manufactured during the development phase is limited. Related to this, another real-life situation discussed in Example 3 below was presented by the researcher during the January 2019 meeting with FDA.

Example 3

A major global vaccine company submitted approximately 8000 PACs in a year, either for prior-approval or via notification mechanisms. This high number of PACs is not atypical for a global pharmaceutical company that has many commercial products each potentially registered in 100+ countries. Of these 8000 changes, more than 99% were approved by the regulatory authorities for implementation; this raised the question:

> *If >99% of the submitted PACs were approved, what could be done through use of a risk-based approach, to reduce the number of changes that had to be submitted to regulatory authorities, such that only the higher risk changes needed to be reviewed for prior-approval?*

Continual improvement and innovation require increased risk tolerance; thus, one ponders would it be possible, without compromising product quality and/or patient safety by implementing the concepts of ICH Q9 and ICH Q10, that only higher risk changes might need prior-approval by regulatory authorities? Then, with fewer PACs requiring prior-approval, coupled with faster regulatory approvals and fewer countries needing to approve each PAC, the global PAC complexity hurdle could be markedly reduced.

In addition to discussing the current complexities with global PAC management and presenting examples that challenge companies in their daily operational work, the researcher and her co-lead discussed with FDA during the January 2019 meeting, ways that pharmaceutical companies could build trust with regulators, so that more changes could be managed in the PQS without requiring prior-approval. This raised the question - what does a pharmaceutical company need to do to be trusted to make PAC decisions in the future without obtaining prior-approval of those PACs which today require that?

The researcher inquired if the FDA would be interested and willing to work with the *1VQ for PAC Initiative* in piloting a shift for several PAC examples, where they were moved from being prior-approval changes to notifications, or to only being managed within a company's PQS. This involved moving towards the vision of science and risk-

based approaches that enabled continual improvement and innovation, and it was in line with the FDA's 21st century vision as described in 2004 and as documented in ICH Q10 Annex 1. The FDA agreed that the current state of complexity could not continue and that a change was essential. They stated that instead of multiple conversations with different industry associations, unified positions and solutions from the pharmaceutical industry would be essential in gaining alignment between companies and regulators. The FDA also emphasized that given the global nature of the problem, other regulatory authorities needed to be included in the discussion. Outcomes of the meeting with FDA are described in section 6.1.5.

In order to fully understand the PAC management landscape and the role of different stakeholders, it is useful to understand the current role of regulatory inspectors in assessing the effectiveness of a company's PQS, and becoming more integral for faster PAC management.

6.1.4 The Role of Inspectors in PAC Management

Within each regulatory authority, regulatory assessors (sometimes also known as reviewers) are responsible for the review and approval of regulatory submissions made by pharmaceutical companies for new products or for PACs to existing commercial products. Regulatory authorities also have regulatory inspectors who are responsible for inspecting (mainly through on-site visits), the quality systems and processes within companies to ensure that they are compliant with regulatory requirements and with the approved regulatory filing for a product. This is to assure that the product manufactured, tested and released by the company has the right quality, efficacy and safety attributes.

Currently, regulatory inspectors do not usually get involved in evaluating submissions for PACs - this is generally the role of regulatory assessors. Similarly, regulatory assessors do not usually get involved in evaluating the quality system and its related processes within a company - this is the role of regulatory inspectors. In some instances, assessors may also be inspectors during pre-approval inspections for a product, but in general, the assessor and inspector roles are distinct and separate within most regulatory authorities. There are typically quite limited interactions between regulatory assessors and inspectors within regulatory authorities. This clear distinction of responsibilities

between regulatory assessors and inspectors, coupled with the limited interactions between the two, while understandable, does result in a sub-optimal situation. This is because each has only a partial and limited understanding of the extent of process knowledge, systems and processes that support the maintenance of a state of control and continual improvement of the manufacturing, testing, release and distribution of a product.

Though PIC/S, which has an excellent knowledge base through its global network of regulatory inspectors, was an observer in the ICH Q12 EWG, there had been very limited detailed discussions on the valuable role that inspectors can (and should) play in assessing the effectiveness of a company's PQS. There is a greater opportunity where inspectors can contribute towards the decision-making on whether or not a particular PAC may be managed within a company's PQS without requiring prior-approval from regulatory assessors.

ICH Q12 states that, while regulatory assessment and inspection should be maintained as complementary and independent activities, timely knowledge and information exchange between assessors and inspectors can facilitate regulatory oversight of product lifecycle management and even reduce submission burdens for the MAH. If a company fails an inspection for critical PQS aspects, that can impact its ability to take advantage of the flexibility offered by ICH Q10 Annex 1 or the ICH Q12 tools. On the other hand, if a company has an effective PQS and can demonstrate during inspections that its PQS is being used to make, document and implement decisions in a manner that assures product quality and patient safety, the company should be allowed reduced reporting for certain PACs, as described by ICH Q10 Annex 1 and ICH Q12. Therefore, inspectors indeed have an important role to play in realising the vision of both of these ICH guidances, even though they do not review and approve specific PACs, which remains the role of assessors.

Towards this end, in September 2018, the researcher had made a proposal to the PIC/S QRM Expert Circle, asking if they would be interested in a collaboration to:

1. Review a pilot on a standard risk-based approach to PACs developed and implemented by companies

2. Have a dialogue with the *1VQ for PAC Initiative* team on what constitutes an effective PQS and how it could be assessed during inspections

This proposal is discussed in section 6.2.1 below. PIC/S responded that they would take this collaboration into consideration. Details on the resulting interactions between the researcher and PIC/S since 2018 are described further in this chapter in section 6.2.

Finally, at the meeting with Dr Woodcock and the senior FDA leaders, the researcher raised this topic and presented the proposal made to the PIC/S QRM Expert Circle. The outcome of this, and all the other dialogue presented above, is summarised in section 6.1.5.

6.1.5 Outcomes of the Meeting with Dr Woodcock and FDA

The discussions with, and the position of, the FDA were encouraging in validating the need for this research. Dr Woodcock and the FDA senior leaders appreciated the global complexity associated with PACs and they acknowledged that no one stakeholder group could resolve this situation through their own solutions; so, they agreed on the urgent need for collaborative solutions to the 'wicked problem' of continual improvement, innovation and shortages. This was further confirmation that solving the 'wicked problem' needed a multi-stakeholder approach and holistic *systems thinking*. Furthermore, the FDA agreed that the current regulatory approval effort being put in by both companies and regulators, was not proportional to the value gained for the patient from the existing regulatory reviews of PACs (this was related to the discussion on the example of greater than 99% of 8000 PACs submitted per year by a company and approved by regulatory authorities; similar percentages were reported by multiple vaccine companies through the *1VQ for PAC* focus groups). The dialogue highlighted the importance and value of using better science and risk-based approaches to enable regulatory resources and oversight to focus on a subset of these PACs – those that represented higher risks to product quality, safety and public health.

The FDA leaders agreed that, in addition to regulatory risk-based guidances, a company's demonstrated product and process knowledge and an effective PQS should be leveraged for PAC categorisation. They suggested that, in order to lower the

activation energy needed to overcome the global complexity hurdle, companies needed to demonstrate their application of product and process knowledge in their risk-based decision-making in daily operations. In addition, companies needed to demonstrate that they had an effective PQS framework that is utilised appropriately to maintain a state of control, document their risk-based decisions for PACs, and ensure management accountability as described in ICH Q10. In their experience, FDA had not seen companies do this well, and they stated that companies demonstrating a deep understanding of their product and processes, and using an effective PQS, was fundamental in gaining trust with regulators.

The FDA recognised that these challenges cannot be solved independently by pharmaceutical companies or their regulators, but that both together needed to find a way to drastically reduce the gap between knowledge gain and knowledge implementation in daily operations. FDA also supported the thinking that an effective PQS was essential for successful implementation of the concepts and tools that ICH Q12 was developing. This required the involvement of both assessors and inspectors, and active interactions between them.

The proposal to PIC/S, described further in this chapter, was well-received by Dr Woodcock and FDA, and they supported the development of practical application PAC examples to be used as a means to improve the dialogue between assessors and inspectors on what an effective PQS may look like, and how it might be leveraged in the regulatory decision-making for PACs.

FDA also expressed that they would be keen and open to hosting and utilising a consortium of regulators from different countries to pilot a joint review (or even a reliance conversation) for PAC assessments and approval. They were willing to help activate the dialogue with regulatory authorities from different countries to come together and work more closely for approval of PACs. As resulting from and committed to at the end of the January 2019 meeting with the researcher and Vinther, the FDA subsequently activated this discussion in 2020 via ICMRA, which is further elaborated upon in section 6.5.

The FDA was very positive on the industry's *1VQ for PAC Initiative* and underscored the importance of operational Quality leaders engaging in developing and implementing global solutions in this area. They were encouraged to see the pharmaceutical industry working on standardisation through the *1VQ for PAC Initiative*, and they expressed a desire to see more of this happening. They strongly encouraged the researcher and Vinther to get involvement, sponsorship and support from senior management within pharmaceutical companies.

One suggestion the FDA made was that the *1VQ for PAC Initiative* should work towards bringing clarity and alignment on how to demonstrate an effective management of PACs within the PQS. To achieve this, FDA indicated it was open to a discussion with Quality heads from pharmaceutical companies on what is an effective PQS and how it could be used for PACs (both from an assessor and inspector perspective). Its goal was to see these elements of an 'Effective PQS for PACs' integrated into the quality culture tools that were in development and under discussion by organisations such as PDA, ISPE, St. Gallen University et. al.., at the time. FDA indicated that it wanted to see practical examples of PACs that could be managed using an effective PQS and a standard risk-based approach. However, before they committed to participation in further discussions with pharmaceutical companies on such examples, they asked for a Concept Paper (which was subsequently delivered by the researcher and Vinther via the *1VQ for PAC Initiative*) to outline:

- The pharmaceutical industry's role in the topic of PAC management, and advancing continual improvement and innovation, since ownership for product quality resides with a company
- What aspects would be included in a practical pilot implementation e.g., standard risk-based approach, how to demonstrate an effective PQS, etc.
- Expectations from FDA and other regulatory authorities for the pilot
- Expected decision and outcomes from the pilot. e.g., FDA accepts the approach, examples etc., for PAC management and could consider participation in specific pilots with the pharmaceutical industry or other regulatory authorities

In general, FDA was supportive of the *1VQ for PAC Initiative* publishing some of the solutions (e.g., standard risk-based approaches, how to demonstrate an effective PQS)

as industry standards – and could consider endorsing those solutions for use by their assessors.

When asked by the researcher and Vinther if the FDA would be willing to jointly partner on such a Concept Paper, they responded that a partnership only with FDA would not be useful in resolving this global issue. FDA indicated that it was open and interested in reviewing and providing feedback on the Concept Paper (which they did once the Concept Paper was developed and before it was finalised and endorsed by the CQOs), but asked that it be a pharmaceutical industry Concept Paper with sponsorship and commitment from senior management of pharmaceutical companies. FDA also offered to continue the dialogue on this topic and to facilitate ongoing and new solution opportunities being discussed with the *1VQ for PAC Initiative* team and with other regulatory authorities.

As the *1VQ for PAC Initiative* has progressed, the researcher and Vinther continued their interactions with FDA, providing updates on progress, seeking feedback, and exchanging on opportunities to advance solutions that could improve the current state and better enable continual improvement, innovation and the mitigation of shortages. Details of these interactions and *1VQ for PAC* solutions are discussed in Chapter Seven and Chapter Eight of this thesis.

6.1.6 FDA ICH Q12 Implementation Guidance and Feedback from the *1VQ for PAC Initiative*

In May 2021, the FDA issued a draft guidance for the industry on ICH Q12 implementation considerations for FDA-regulated products (FDA, 2021). The guidance clarifies how the ICH Q12 tools and enablers can be implemented within the US regulatory system. The FDA solicited comments on the draft guidance by July 2021.

The researcher and Vinther developed draft comments on the guidance and solicited further input from the *1VQ for PAC Initiative* team. The comments were finalised and sent to the CQOs sponsoring the *1VQ for PAC Initiative* for review, input and endorsement.

The overall position and comment submitted by the *1VQ for PAC Initiative* was that the clear and comprehensive guidance was welcomed by the pharmaceutical industry especially in relation to the science and risk-based assessment of individual PACs and the ability to manage more PACs within the PQS only, by applying the principles of ICH Q10 and ICH Q9. Several suggestions were provided, such as referencing the published PIC/S Recommendation Paper on "*How to Evaluate and Demonstrate Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management"*, emphasising the importance of interactions between assessors and inspectors in realising ICH Q12, and the vision of regulatory flexibility through utilisation of an effective PQS.

6.2 The Pharmaceutical Inspection Cooperation Scheme (PIC/S)

PIC/S is a non-binding informal cooperation agreement between 53 participating regulatory authorities on GMPs for human and veterinary medicinal products. PIC/S was established in 1995 as an extension of the Pharmaceutical Inspection Convention (PIC) that was founded in 1970 by the European Free Trade Association (EFTA). PIC was founded with the goals to advance mutual recognition of inspections, harmonisation of GMP requirements, achieve uniformity of inspection systems, training of inspection, exchange of information and mutual confidence and trust.

After 1993 it was not possible to add new members to PIC, because, under EU law, only the European Commission could authorise signing agreements with other countries, and expansion of PIC was not possible until the European Commission became a member of PIC. Therefore, in November 1995 it was decided to develop PIC/S. PIC and PIC/S would operate in parallel; so, since November 2004, PIC/S is officially registered as an Association under Swiss Law with the "Registre du Commerce" (Trade Registry) of the Canton of Geneva (http://rc.ge.ch/). Its official name is "Pharmaceutical Inspection Co-operation Scheme - Association de Droit Suisse".

PIC/S' mission is to:

> *"lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products."* (PIC/S, 1995)

This is achieved through harmonised GMP standards and guidance documents, training Competent Authorities, particularly GMP inspectors, assessing or reassessing GMP inspectorates, and facilitating cooperation and networking between Competent Authorities and international organisations. Before any regulatory authority becomes a member (or as officially known, a Participating Authority) of PIC/S, they are assessed for equivalence in relation to their GMP guidance and legislation. The number of participating authorities in PIC/S has increased from 10 when it started, to 53 as of 2020.

PIC/S is one of the few regulatory organisations that achieves harmonisation of GMPs and inspections at a global level through Expert Circles, Working Groups, training of inspectors, and joint visits programme. The PIC/S organisational setup includes an overall PIC/S Committee of Representatives from the Participating Authorities, which supervises seven sub-committees on various topics (PIC/S, 2020). The PIC/S Committee is the decision-making body, and decisions are made unanimously. One of the seven sub-committees is the Sub-Committee on Expert Circles (SCEC), which reviews the composition, functioning, activities and mandates of all the PIC/S Expert Circles. The Executive Bureau steers the PIC/S organisation between meetings, and the Secretariat supports the Committee, Sub-Committees, Executive Bureau and the Participating Authorities in executing their responsibilities.

PIC/S is the only global organisation that deals exclusively with GMP. In addition to having Participating Authorities as members, PIC/S also interacts with other pharmaceutical industry and professional organisations, such as ICH, International Federation of Pharmaceutical Manufacturers' Association (IFPMA), PDA, ISPE, etc., such as soliciting input and comments during the development of PIC/S documents. With the increasing globalisation of both the pharmaceutical industry and regulatory requirements, PIC/S' role has become increasingly important and valuable in internationally harmonising GMP and regulatory requirements, inspecting for and evaluating GMP compliance, licensing manufacturing sites, and increasing information exchange between regulatory authorities. The primary mechanism that PIC/S uses to drive GMP harmonisation is through its own GMP Guide, as well as its related guidance documents, Q&As, recommendation papers and aide-memoir documents for the pharmaceutical industry, inspectorates and inspectors. PIC/S' global harmonisation

work has provided direct benefits not only to the participating regulatory authorities, but also to the pharmaceutical industry, through reduced duplication of inspections, enhanced market access, export facilitation and in general, higher confidence in medicines manufactured in countries where the regulatory authority is a participating PIC/S authority.

6.2.1 Discussions with PIC/S QRM Expert Circle

Per the PIC/S organisational structure, PIC/S Expert Circles facilitate discussions and exchange of ideas and experiences on specific topics among inspectors, which can result in draft guidance, recommendations, and training events. One of the eight current PIC/S Expert Circles with is the QRM Expert Circle, chaired by Dr Kevin O'Donnell from the HPRA in Ireland. It was established in 2007 and has developed QRM implementation models for inspectorates, guidance documents and basic and advanced training programmes for inspectors on how to inspect and assess QRM implementation at pharmaceutical companies.

Prior to embarking on this specific inquiry, the researcher primarily interacted with the PIC/S QRM Expert Circle for PIC/S in relation to QRM training activities, as noted in Appendix I of this thesis. Further interactions with PIC/S occurred for the development of one of the solutions in scope of this research study, described in Chapter Eight, section 8.4 of this thesis.

As described in Appendix I, the researcher had thus far participated as a trainer in three advanced PIC/S QRM training workshops for GMP inspectors since 2015, being the only trainer invited from a pharmaceutical company to these inspector-only training sessions. PIC/S workshops are typically closed to pharmaceutical industry participation, and the researcher was invited in her capacity as a QRM expert and not as a pharmaceutical industry representative. Each training event were attended by 70-80 inspectors per session from almost all PIC/S member countries and WHO. This inspector training aspect of the researcher's activities with PIC/S is not being further elaborated upon in this thesis as they were not directly related to this research study. The PAC management related interactions with PIC/S are the most relevant, and are described further in the next section.

6.2.2 Initiating Activities with PIC/S QRM Expert Circle on Advancing Role of Inspectors in Transforming PAC Management, September 2018

At the third PIC/S QRM advanced training event, which was held in Taiwan in September 2018, the researcher was invited to join the QRM Expert Circle closed session to discuss the further development of the Expert Circle QRM training programmes for GMP inspectors. At this closed session, the researcher was given time on the agenda to specifically present on the topic of utilisation of risk-based approaches to improve PAC management. The researcher presented a proposal for a possible collaboration with the PIC/S QRM Expert Circle, on how the pharmaceutical industry might be incentivised to continually improve their processes and products and thus reduce risks to patients. This led to a discussion on ways to reduce PAC complexity and increase innovation by pharmaceutical companies.

It was suggested by the researcher, based on her PAC work conducted to date, that a risk-based approach and an effective PQS could provide a means to manage more PACs in the PQS without requiring prior-regulatory approval. The concept of using PAC risk assessments as part of regulatory submissions in order to reduce review redundancies by each regulatory agency involved was explored. In addition, it was proposed that data-driven risk assessments could also be used to demonstrate when a PAC does not increase risk to product quality and/or patient safety and therefore, could be implemented faster through the PQS only, without a regulatory prior-approval submission; this would also facilitate the timely implementation of new product and process knowledge. The researcher suggested that practical application of this proposal would involve performing a structured and standard risk assessment for each PAC, and the shift that could be expected in risk-based decision-making for PACs was presented in a diagram developed by the researcher, as shown in Figure 6.3.

Figure 6.3: Standard PAC Risk Assessment Submitted to Each Country

The left-hand side of the diagram depicts the current situation, which results in individual submissions to regulatory bodies globally. The right-hand side presents a situation where one risk assessment for each change is reviewed by all regulatory authorities, who could in turn each use this to determine if they accept the conclusions of the PAC risk assessment, and also, whether or not they could rely on the effectiveness of the company's PQS to be satisfied that no prior-approval for the PAC is required.

The researcher proposed that an effective PQS, which included a means for the comprehensive science and risk-based assessment for PACs and which managed new knowledge in a timely manner, could be a foundational lever to achieve the objective of reliably producing high quality products. It could also provide a mechanism to realise the vision laid out in ICH Q10 Annex 1:

> *"Opportunity to facilitate science based pharmaceutical quality assessment and optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement" by "demonstrating effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles."* (ICH, 2008)

In order to achieve this, the importance of assessing the PQS of a company for its effectiveness was highlighted, and this was where pharmaceutical inspectors could play a key role. This was the primary reason which led to the researcher bringing this topic for discussion to the PIC/S QRM Expert Circle as it developed its training programmes for inspectors.

The pharmaceutical industry *1VQ for PAC Initiative* was presented to the PIC/S QRM Expert Circle, in particular the work underway on the development of a standard risk-

based approach, which was intended to be implemented consistently across the pharmaceutical industry.

The researcher inquired if the PIC/S QRM Expert Circle would be interested in:

1. Reviewing a pilot on a standard risk-based approach for PACs developed and implemented by companies
2. Engaging in a dialogue on what constitutes an effective PQS and how it could be assessed during inspections – possibly developing guidance for the pharmaceutical industry about what attributes constitute an effective PQS for management of PACs
3. Consider developing guidance for inspectors on how the effectiveness of the PQS could be assessed during an inspection

The concept of a standard risk-based approach for PACs across the pharmaceutical industry was supported by the participants, and there was agreement that the PIC/S QRM Expert Circle would be the right PIC/S group to discuss the risk-based approach with inspectors, since it was probably the largest and most active forum for GMP inspectors from PIC/S member countries. It was acknowledged that PQS effectiveness is a dynamic state - things such as changes in management, loss of key personnel, etc., could also affect PQS effectiveness. So, beyond inspections, other mechanisms such as Quality System Management Review were important to ensure continued PQS effectiveness. The participants indicated they would consider these suggestions and that the Coordinating Committee of the Expert Circle would revert to the researcher on the proposal made in relation to reviewing the pharmaceutical industry's standard risk-based approach for assessment of PACs, and developing guidance for the pharmaceutical industry about what constitutes an effective PQS. In addition, the Coordinating Committee would also consider developing guidance for inspectors on how the effectiveness of the PQS could be assessed during GMP inspections.

This was a productive discussion and it had an encouraging outcome for the researcher, with PIC/S acknowledging the need to improve the risk-basis of PACs, and how the QRM Expert Circle could have a meaningful role to play in this area. The discussion also demonstrated a high level of openness to evaluating what the Expert Circle might do to contribute to this topic.

6.2.3 Understanding the Spirit and Intent of GMP Requirements on Change Control

Post-meeting, Dr Kevin O'Donnell, Chair of the Expert Circle, suggested exploring integration of QRM specifically into the change management system, since that PQS element is core to PAC management. Thus, the researcher commenced a study of GMP requirements on Change Control, with the objective of understanding the intent and spirit behind those requirements. In particular, the following documents were explored for this study:

- EU GMP Guide, Annex 15
- ICH Q10: Change Management System
- ICH Q12: Appendix 2: Principles of Change Management
- PIC/S GMP Guide on Medicinal Products, Chapter 1, PQS
- PIC/S GMP Guide on Medicinal Products, Chapter 5, Production
- PIC/S GMP Guide on Medicinal Products, Chapter 6, QC
- PIC/S GMP Guide on Medicinal Products, Chapter 7, Outsourced Activities
- EU GMP Guide Part II (i.e., ICH Q7)

This review also included detailed discussions on Change Control within the *1VQ for PAC Initiative* team. The review and discussions emphasized that the spirit and intent of these GMP requirements for change control was that - as knowledge increases during the life of a product, changes are inevitable, so the change control system should ensure the validated state, and a state of control is maintained even as changes are made. Control of changes is an important part of KM, and QRM should be used to evaluate the need, potential impact and effectiveness of a change.

This piece of work led the researcher to further advance the initially developed considerations on change management, by exploring the development of a checklist-based approach that could aid in distilling the considerations for risk-based change management into a tangible, actionable, easy-to-implement tool that not only met documented GMP requirements, but also met their spirit and intent.

6.2.4 Researcher's Proposal to the PIC/S QRM Expert Circle, April 2019

A follow-up discussion with the PIC/S QRM Expert Circle took place at the HPRA office in Dublin in April 2019. It confirmed that the focus of this research should be on the integration of QRM into the change management system, with the intent of supporting continual improvement and innovation, while also ensuring that a state of control was maintained. At this meeting, the researcher proposed the development of a document that could be used by the pharmaceutical industry as a tool and a reference, demonstrating what a good risk-based change management system could look like and how its effectiveness might be demonstrated during inspections. Figure 6.4 (ICH, 2008) illustrates the specific areas of focus from the ICH Q10 diagram (highlighted with the red boxes).

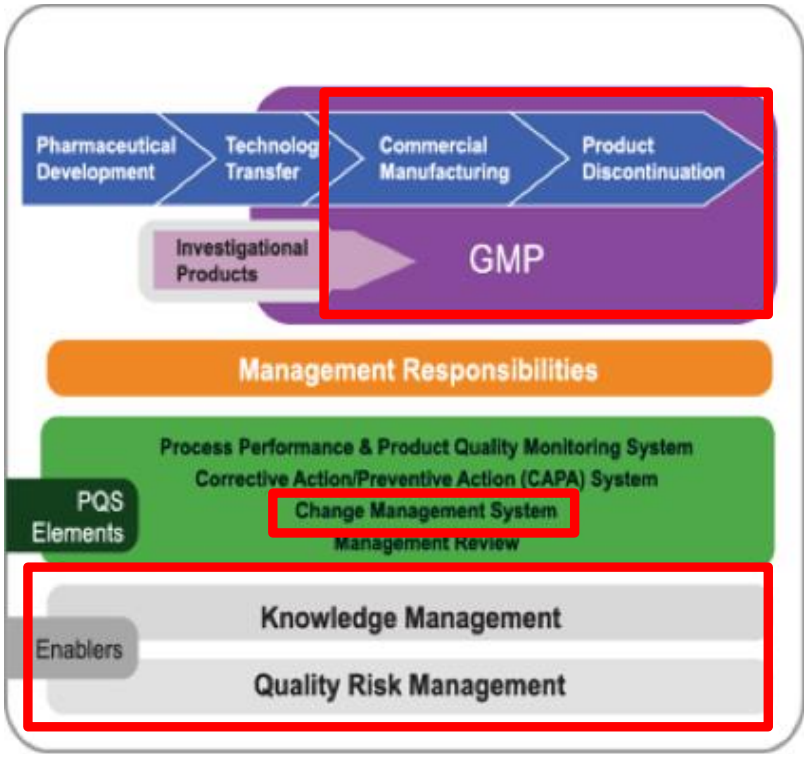

Figure 6.4: Targeted Discussion on Risk-Based Change Management System with the PIC/S QRM Expert Circle (ICH, 2008)

The discussion was framed in the context of 21st century manufacturing paradigms and innovative therapies (such as personalised medicines, Advanced Therapy Medicinal Products (ATMPs)), which require a complete revision of the pharmaceutical industry's

traditional manufacturing paradigm. In order to achieve the objective of reliably producing high quality products, the pharmaceutical industry needs to implement new knowledge in a timely fashion and continually improve and innovate **without increasing risk to the patient**. Manufacturing of the future must become efficient, flexible and agile, to adapt to rapidly changing demands and meet evolving patient needs. Meanwhile, improvements need not compromise the quality and availability of therapies. This implies the use of innovative manufacturing and supply approaches and cutting-edge technologies. It requires overcoming challenges and barriers to their implementation. The need to revolutionise the technical sector was recognised almost 2 decades ago by the pharmaceutical industry, ICH and regulatory authorities such as FDA, when the first therapies based on recombinant monoclonal antibodies were showing significant benefits for patients. Shortly thereafter, work was started to develop harmonised guidelines outlining risk- and science-based approaches to product development and manufacturing. ICH Q8-Q11 were published between 2005 and 2011, and included new, paradigm-changing concepts such as 'Quality by Design' (QbD).

Per the FDA guidance for industry on Quality Systems Approach to Pharmaceutical cGMP regulations:

> *"effective change control activities (e.g., quality planning and control of revisions to specifications, process parameters, procedures) are key components of any quality system. In this guidance, change is discussed in terms of creating a regulatory environment that encourages change towards continual improvement. This means a manufacturer is empowered to make changes subject to the regulations based on the variability of materials used in manufacturing and process improvements resulting from knowledge gained during a product's lifecycle."* (FDA, 2006)

With all this in mind, a discussion on the ICH Q10 Annex 1 (ICH, 2008) shown below in Table 6.1 which stated several potential opportunities to enhance regulatory approaches, took place with the PIC/S QRM Expert Circle.

Table 6.1: ICH Q10 Annex 1 - Potential Opportunities to Enhance Science and Risk-Based Regulatory Approaches (ICH, 2008)

Scenario	**Potential Opportunity**
1. Comply with GMPs	Compliance – status quo

2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk-based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: • facilitate science based pharmaceutical quality assessment; • enable innovative approaches to process validation; • establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk-based approaches for regulatory inspections; • facilitate science based pharmaceutical quality assessment; • optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement; • enable innovative approaches to process validation; • establish real-time release mechanisms.

The discussion reiterated that the intent and spirit of cGMP requirements on change control must be met.

It was agreed that structured and evidence-based risk reduction could enable faster implementation of changes that reduced risk to patient safety, product quality and product availability. The researcher, together with Dr O'Donnell, presented a vision of what evidence-based risk reduction is and how it could be used within a continual improvement framework (Ramnarine and O'Donnell, 2018). A structured risk assessment for each change should enable rigorous assessment, planning, categorisation and implementation of a change. A science and data-driven basis for the risk assessment could help assess whether a change might increase risk to product quality and/or patient safety. Where the risk assessment showed that the change did not increase such risk, it could and should enable faster implementation and management of the change entirely within the PQS, thus allowing the timely implementation of new knowledge.

In April 2019, the researcher presented to the Expert Circle, a draft checklist on QRM application for change management. This checklist had been developed by the researcher and was further refined with Dr O'Donnell prior to bringing it for discussion

to the Expert Circle. An overview of the draft checklist is depicted in Figure 6.5, developed by the researcher and O'Donnell.

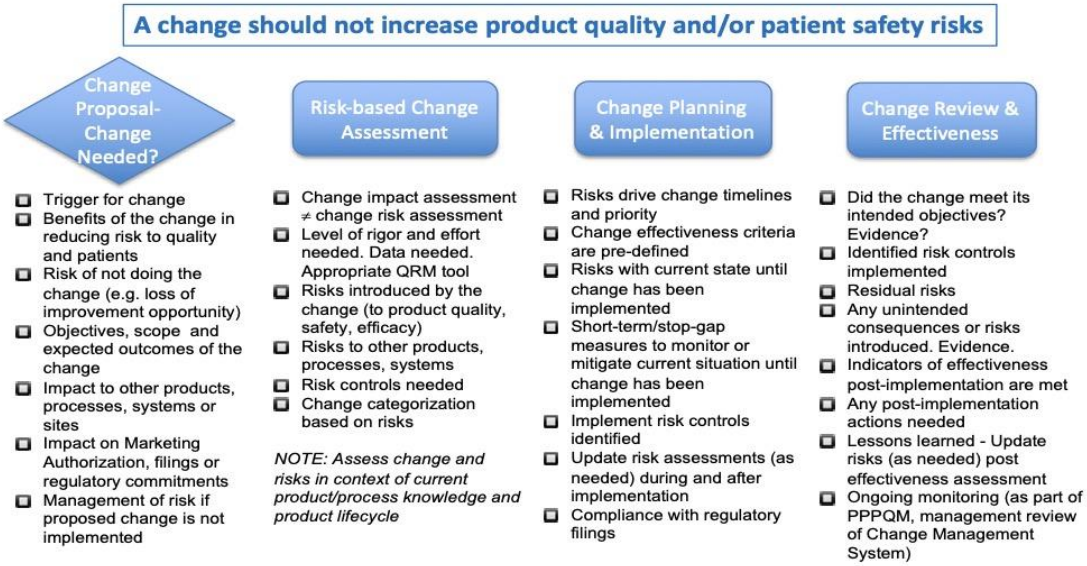

Figure 6.5: Structured QRM Application Checklist for Change Management for PIC/S QRM Expert Circle Discussion

The checklist approach, which was developed essentially to serve as a potential tool and solution for supporting PAC management that required prior-approval, in accordance with the vision of ICH Q12 and Annex 1 of ICH Q10, received positive comments from the Expert Circle; there was a very productive discussion on the contents of the checklist, and the Expert Circle agreed to review and provide detailed comments on the checklist in order to continue to develop it further. Agreement was achieved at that April 2019 meeting that the checklist could become useful guidance for inspectors on how to assess the effectiveness of risk-based change management activities during inspections of pharmaceutical companies. The Expert Circle agreed to discuss and decide on next steps for the checklist. The checklist eventually became one of the published PAC solutions that is key for implementation of ICH Q10 and ICH Q12, and is described in Chapter Eight, section 8.4 of this thesis.

6.3 European Commission (EC)

6.3.1 Research-related Contribution to the EC's Pharmaceutical Strategy for Europe 2020

In November 2020, the European Commission (EC) published a Pharmaceutical Strategy for Europe that aimed at:

> *"creating a future proof regulatory framework and at supporting industry in promoting research and technologies that actually reach patients in order to fulfil their therapeutic needs while addressing market failures. It will also take into account the weaknesses exposed by the coronavirus pandemic and take appropriate actions to strengthen the system.*" (European Commission, 2020)

The strategy was built on four pillars:

1. Ensuring access to affordable medicines for patients
2. Supporting competitiveness, innovation and sustainability of the pharmaceutical industry
3. Enhancing crisis preparedness and response mechanisms, diversified supply chains and addressing medicines shortages
4. Ensuring a strong EU voice in the world

One of the elements of the third pillar was a *"sound and flexible regulatory system*" that enables regulatory efficiency, simplifies and streamlines procedures, and brings EU regulatory approval timelines on to par with other parts of the world. A flagship initiative on regulatory efficiency is revising the EU variations framework to *"make the lifecycle management of medicines more efficient and adapted to digitalization"*.

The researcher and Vinther, on behalf of the *1VQ for PAC Initiative*, provided specific feedback to the EC in September 2020 on the Pharmaceutical Strategy for Europe, specifically on aspects related to PAC management and flexible and efficient regulatory processes. So, it was encouraging to see the Commission acknowledge the need to modernise, via a more flexible and efficient regulatory system, and the action to make legislative and non-legislative updates to the EU variations regulations and processes called out as a flagship initiative.

6.3.2 Research-related Contribution to the EC's Structured Dialogue on Security of Medicines Supply Initiative

The COVID-19 crisis highlighted the need for enhanced resilience and security in medicines supply. Enhanced resilience and supply security are clear objectives of the EC's Pharmaceutical Strategy for Europe, adopted in November 2020.

To this end, in February 2021, the EC launched a Structured Dialogue Initiative with the intent to:

> *"strengthen the resilience of pharmaceutical supply chains and ensure the security of supply of medicines, without compromising the affordability of medicines."* (European Commission, 2021)

Four specific workstreams were initiated – Robust Supply Chain, Critical Medicinal Products, Vulnerabilities and Innovation – and each was chartered to collect data and sound evidence, analyse it, share perspectives and produce a report by July 2021 with concrete measures to strengthen the resilience of pharmaceutical supply chains and ensure security of medicines supply to patients in Europe. Workstream 3, on Vulnerabilities, was scoped to identify the most frequent disruption challenges that threaten medicines supply, drivers of these vulnerabilities at various stages in the supply chain, and the potential financial impact of addressing those challenges and drivers.

The researcher and Vinther worked with the CQOs sponsoring the *1VQ for PAC Initiative* to identify three Qualified Persons (QPs) from Abbvie, Sanofi and Takeda, to participate on Workstream 3, on Vulnerabilities, and in doing so, they would contribute to the discussions related to regulatory requirements, by raising the issues pertaining to the high level of global regulatory complexity associated with PAC management and supply. The draft report was submitted to the EC in July 2021. It stated that:

> *"a vulnerability in the supply of medicines is a risk that might cause challenges in access to medicines"*

and it identified the following four aspects that lead to vulnerabilities:

1. Consolidation of the supply chain and investments in manufacturing capacity linked to cost pressures

2. The degree of geographical diversification for certain pharmaceuticals, raw materials or technologies
3. Regulatory complexity and degree of regulatory convergence
4. Degree of visibility on supply and demand

On the third aspect, related to regulatory complexity, the report states:

> *"With relevance for all products, there is the need to improve the regulatory efficiency associated with Post Approval Changes (PACs). PACs are inevitable and necessary throughout the life of a drug product to implement new knowledge, maintain a state of control, and drive continual improvement which serves to enhance product quality and ultimately benefit patients. To better serve patients, PACs should be managed in a timely manner. However, today many PACs (including low risk changes) require prior regulatory approval that can take up to five years before full implementation worldwide. Standardizing regulatory procedures across the EU and globally, and leveraging a risk-based approach to post-approval changes, would decrease supply chain vulnerabilities."*

Though not published yet, Annex B of the report elaborates on the global regulatory complexity issue, and it includes direct input from the *1VQ for PAC Initiative*.

As expected of a 'wicked problem' and reaffirmed by the workstream, the report clearly acknowledges that stakeholders involved in the work had divergent views and position, and it was not possible to get consensus on all aspects of the report. Nevertheless, securing general agreement within the drafting group on the above text for the Vulnerabilities section of the report was a significant achievement for this research work and the *1VQ for PAC Initiative* – as perhaps for the first time, it was agreed that the issue of regulatory complexity affecting PAC management and continual improvement needed to be highlighted in an official publication as a contributor to the problem of supply chain vulnerabilities and ultimately medicines shortages.

6.4 World Health Organisation (WHO)

The WHO founded in 1948, is a specialised agency of the United Nations responsible for international public health. It connects nations, partners and people to promote health, keep the world safe and serve the vulnerable – so everyone, everywhere can attain the highest level of health. The World Health Assembly (WHA) is the decision-

making body of WHO, attended by delegations from all WHO Member States; it focuses on a specific health agenda prepared by the Executive Board.

6.4.1 WHO's Reliance Practices

As a general operating principle, the WHO has supported reliance between regulatory authorities in order to optimise the utilisation of available resources and expertise, and avoid duplication of efforts, thereby allowing National Regulatory Authorities (NRAs) to focus their efforts on value-added regulatory activities that cannot be performed by another authority. The WHO is one of the more advanced agencies in acknowledging that the complexity of regulatory oversight activities can be addressed *"through innovative and more effective forms of collaboration including reliance*". As a part of a 'smart regulation' initiative, it encourages Good Reliance Practices as a component of Good Regulatory Practices, QAS/16.686 (WHO, 2016b).

In 2020, WHO issued draft working document QAS/20.851 on Good Reliance Practices that provides guidance, definitions, key concepts, and considerations to guide reliance activities between NRAs (WHO, 2020). The guidance defines reliance as:

> *"the act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others."* (WHO, 2020)

It makes an important distinction between reliance and recognition, whereby recognition is:

> *"the acceptance of the regulatory decision of another regulatory authority obviating the need for additional regulatory assessment in reaching one's own decision."*

The WHO's six key principles that underpin good reliance practices are:

1. Universality (reliance applies to all NRAs irrespective of their levels of maturity or resources
2. Sovereignty of decision-making (reliance does not imply dependence or giving up accountability for regulatory decision-making)
3. Transparency (regarding standards, processes and approaches for reliance)
4. Respect of national and regional legal basis

5. Consistency in application of pre-determined categories for products or processes, and
6. Competency for critical decision-making

As part of the considerations in implementing reliance, the guidance highlights the role the pharmaceutical industry must play in strictly adhering to the factors that make reliance possible, such as when filing applications in multiple countries. Several barriers were outlined, including a lack of accessible information (such as a company's proprietary knowledge being shared across countries), and maintaining confidentiality of non-public information.

This was the first instance the researcher noted of a regulatory authority clearly recognising and acknowledging that a "one size fits all" approach is not workable, that a culture and mindset shift towards innovative and more effective ways of working, based on trust is essential, and that convergence or harmonisation of requirements or standards, and information-sharing and dialogue between regulators are important enablers.

6.4.2 Collaboration Proposal to WHO from the *1VQ for PAC Initiative*

The vision, guidance, principles and considerations laid out in the WHO's QAS/20.851 publication led the researcher and Vinther to seek a meeting in March 2021 with Dr Samvel Azatyan (Team Lead Regulatory Convergence and Networks at the WHO), along with other regulators at the WHO. The meeting was productive, and it resulted in the researcher and Vinther making a collaboration proposal to the WHO in relation to PAC management in the context of the WHO' reliance initiative. Aligned with the research objectives, the proposal focused on the utilisation of two dimensions - science and reliance - to reduce regulatory complexity and improve medicines supply for patients, as depicted in Figure 6.6.

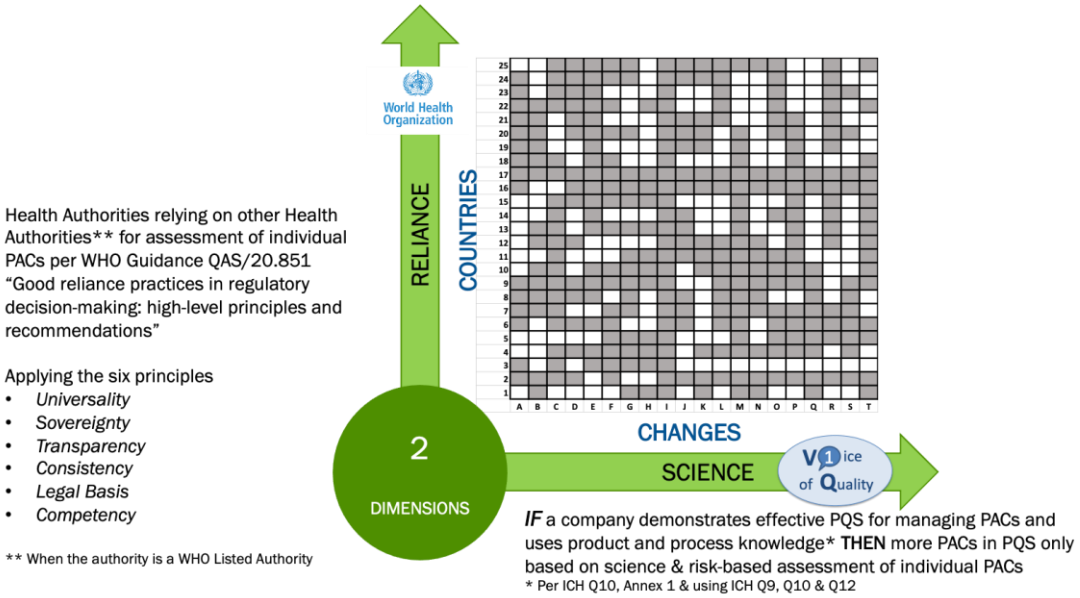

Figure 6.6: Reducing Global Regulatory Complexity Through Science and Reliance

The contextual framework for the *1VQ for PA*C proposal was getting to an environment that was closer to real-time implementation of PACs, and it utilised the following three levers:

1. Timely assessment of PACs by regulatory authorities. This was where each NRA assesses and makes its decisions on PACs requiring prior-approval within 6 months. This could be made possible by regulatory authorities eliminating regulatory procedures that extended overall PAC assessment timelines (the proposal offered that the *1VQ for PAC Initiative* could publish data on the percentage of PACs that were decided on within 6 months across all relevant countries).
2. Regulatory reliance among the WHO Listed Authorities for individual PACs that had been assessed in accordance with the WHO guidance QAS/20.851. The proposal also advocated for consistency in the reporting level and in the documentation requirements for different types of PACs across the NRAs, using the WHO guidance as a starting point.
3. Science and risk-based assessment of individual PACs, and the management of low-risk PACs within an effective PQS without regulatory prior-approval. Management Review activities at the company and reviews by regulatory

authorities during inspections were proposed as the means to assess the effectiveness of the PQS for PAC management.

The WHO was very supportive of the *1VQ for PAC* proposal and of the concept of using increased reliance in the management of PACs by NRAs; this tied in well with the WHO's published Good Reliance Practices document (WHO, 2020). The WHO stated that reliance with respect to PACs had been implemented already in several ongoing initiatives, such as where NRAs were proactively informed of PACs that had been approved for pre-qualified products (the WHO's Prequalification Programme relies on PAC decisions made by what is termed a 'Stringent Regulatory Authority (SRA)'; this applies to products originally approved by SRAs who were recognised by the WHO's Prequalification Programme). As one of the first steps in for the collaboration with the *1VQ for PAC Initiative*, the WHO indicated to the researcher and Vinther that it intended to map out the existing reliance frameworks for PACs between NRAs in different regions. The WHO indicated that a situation in which an NRA exercised full reliance on the PAC assessments by other regulatory authorities when dealing with PACs itself would allow the best use of resources at that NRA, but it also acknowledged that this would represent a significant shift in PAC management activities, given most NRAs at that time performed their own assessment of PACs, and therefore it would take time to change the mindset and culture. It suggested a pilot project for a defined scope of products, where willing NRAs could be considered to serve as a test case and to facilitate a larger roll-out of the proposed approach.

Further definition and scoping for the pilot with the WHO will continue as part of the *1VQ for PAC Initiative*.

6.5 International Coalition of Medicines Regulatory Authorities (ICMRA)

ICMRA is a voluntary, executive-level, strategic coordinating, advocacy and leadership entity of regulatory authorities. ICMRA provides a forum for its member authorities to work together in order to:

- address current and emerging human medicine regulatory and safety challenges globally, strategically and in an ongoing, transparent, authoritative and institutional manner
- provide direction for areas and activities common to many regulatory authorities' missions
- identify areas for potential synergies
- wherever possible, leverage existing initiatives, enablers and resources.

ICMRA provides a global architecture that supports enhanced communication, information sharing and crisis response among and by its member regulatory authorities, and it also addresses regulatory science issues. Currently, 35 medicines regulatory authorities from every region in the world are ICMRA members, with the WHO as an observer.

As a follow-up to the January 2019 discussion and direction from the FDA, as described in Chapter Six, section 6.1, the researcher and Vinther continued regular exchanges with Dr Theresa Mullin, FDA CDER's Associate Director for Strategic Initiatives. Dr Mullin had been assigned by Dr Woodcock as the FDA lead to activate discussions and collaborative solutions among global regulatory authorities in relation to improving reliance and agility in PAC management. The exchanges between the researcher, Vinther and Dr Mullin included her seeking, and acquiring, a deeper understanding of the operational challenges that companies faced when proposing and implementing PACs, especially those affected by regulatory complexity and long assessment timelines. She sought specific input from the *1VQ for PAC Initiative* on topics such as establishing a global quality dossier, the use of standard IT platforms for electronic sharing of information between a company and multiple regulatory authorities, and between regulatory authorities.

Dr Mullin leveraged the wicked problem and the global regulatory complexity framing that had been provided by the researcher and Vinther, to establish a case for change in ICMRA; and in this regard, the researcher's work was cited in a confidential *ICMRA Reflection Paper* on this topic. While the Reflection Paper cannot be disclosed outside of ICMRA, Dr Mullin shared it with the researcher and Vinther, acknowledging that this research and the work of the *1VQ for PAC Initiative* were foundational for the

development of the ICMRA paper and in convincing ICMRA of this case for change. The section below presents the outcome of the work driven by Dr Mullin within ICMRA.

6.5.1 Influencing ICMRA's Strategic Initiative - Global Pharmaceutical Quality Knowledge Management System (PQKMS): Enhancing Regulatory Reliance and Agility

In June 2021, ICMRA announced a global initiative on a Pharmaceutical Quality Knowledge Management System (PQKMS). It had the objective of improving efficiencies and agility across regulatory authorities through common procedures, guidelines, requirements and infrastructure that facilitated reliance and timely sharing of PAC-related information among regulators (ICMRA, 2021).

This was the first-time regulators had collectively acknowledged the global supply challenges that pharmaceutical companies faced due to the delayed implementation of PACs, and they recognised the need for a coordinated Pharmaceutical Quality Knowledge Management capability that would ensure timely and complete information access and assessment of pharmaceutical quality management and risk management capabilities. The following is an excerpt published by ICMRA which demonstrates its thinking in this area:

> *"ICMRA recognizes that regulatory authorities can gain efficiencies by developing common procedures, guidelines, requirements, and interoperable infrastructure that would facilitate the timely sharing of information among regulators on changes occurring within the supply chain. This may include reliance on the assessments of other regulators reviewing those changes. ICMRA considers that this could lead to more timely availability of medicinal products for patients by shortening approval timelines."*(ICMRA, 2021)

The desired state envisaged by ICMRA included standards for review among regulators ("*Enabling more extensive mutual reliance among regulators through work to harmonize specific data expectations for sponsors and* ***standards for review among regulators****, so that regulators can be assured of the comparability of the assessments and related determinations of other regulatory authorities on whom they intend to rely")*, standardised and structured electronic formats that would facilitate rapid assessments of PACs, secure and timely sharing of information among regulators,

harmonisation of submission requirements and data expectations (in a manner that could eventually support simultaneous PAC submissions to all relevant regulatory authorities), and increased mutual reliance between regulatory authorities.

True to the nature of a 'wicked problem' that requires involvement from multiple stakeholders to design and implement solutions, ICMRA recognised that this work was strategic, transformative, that it would take time, and require a multi-stakeholder approach involving regulators, legislators and the pharmaceutical industry.

In summary, parallel progression of this research and continued exchange with key regulatory authorities, as described in this chapter, has served to raise awareness of this wicked problem among the various stakeholder groups, and it has helped advance discussions to identify opportunities for collaborative solutions within the pharmaceutical industry, within the regulatory authorities' community, and between regulatory authorities and the pharmaceutical industry.

Part Four: Unifying the Pharmaceutical Industry

Part Four provides an overview on how the researcher brought the pharmaceutical industry together to create deeper awareness and understanding of current state challenges in assuring a reliable supply of safe, effective, high-quality medicines for patients due to inadequate continual improvement and innovation.

It discusses how the researcher established a unified *One-Voice-of-Quality (1VQ) for PAC* pharmaceutical industry platform for the development of practical solutions that could be consistently implemented with respect to PAC management (Chapter 7).

This represents an important segment of the body of work undertaken in this research study.

Chapter Seven

The Importance of Bringing the Pharmaceutical Industry Together

The pharmaceutical industry plays a multi-dimensional role on the broader topic of drug shortages relating to manufacturing, quality and supply chain issues. Through the course of this research and, while exploring the position of various regulatory authorities as described in Chapter Six of this thesis, it became evident that the pharmaceutical industry had to play a crucial role in the development and implementation of standard global solutions in this area. As many drug shortages originate in the manufacturing and supply processes that are within the scope and responsibility of pharmaceutical companies, many mitigations and controls fall within the remit and responsibility of these companies. However, for the effective implementation of controls, regulators and other stakeholders in the supply chain also have a critical role to play.

Patients rightfully expect that medicines are produced and controlled consistently using modern, or even state-of-the-art technologies, processes, and test methods. This implies that manufacturing facilities, process controls and analytical test methods must be continuously improved and updated over a drug's entire lifecycle, in line with advancing science and evolving technology. This also aligns with the primary objectives of ICH Q10 of product realisation, maintaining a state of control and continual improvement. However, due to the complexity of the regulatory process, it is common for pharmaceutical companies to 'lock in' their manufacturing processes, equipment and test methods, rather than innovate and continually improve them through the commercial lifecycle of a product.

There are multiple barriers to innovation during lifecycle management of a product, and as discussed earlier, one is the complexity of the current PAC management environment. Most changes in processes, methods, facilities, and equipment apply to medicines that are distributed globally. Yet regulatory requirements related to PAC implementation (including the assessment of impact to product quality, safety, and efficacy) are mainly established on a local or national level. With these requirements

varying significantly from country to country in terms of reporting levels, reporting requirements, documentation needed, and approval timelines, globally applicable PACs become a logistical challenge that require excessive time and resources to see them to completion. This discourages innovation as well as increases the risk of drug shortages, supply mistakes and noncompliance situations.

While drug shortages remain as the underpinning theme for this research, this part of the study explores the role of the pharmaceutical industry in developing and implementing solutions to overcome the challenges and complexities associated with driving innovation and continual improvement. Without this, pharmaceutical companies cannot make a meaningful impact and contribution towards reducing drug shortages.

While focusing on the role of pharmaceutical companies in this chapter, the researcher does not intend to underestimate that other stakeholders, including regulators, play in identifying and working towards meaningful solutions for their sector of activities. As is true for a 'wicked problem', many solutions, even if not jointly designed by the different stakeholder groups, will require active dialogue, engagement and collaboration for implementation, if they are to make the much-needed difference for patients.

This chapter focuses on:

- Pre-PhD research activities that were foundational to the design of this research study and its hypotheses as described earlier in Chapter Three of this thesis
- Research focus, where a case for change was made with the CQOs of 20+ global pharmaceutical companies, and which led to the inception of the *1VQ for PAC Initiative*.

7.1 Pre-Research Activities Foundational to Unifying the Pharmaceutical Industry

Advancing the activities that resulted from the drug shortages work and the PDA Technical Report 68 on barriers to continual improvement and innovation, the researcher started a deeper exploration into the hurdles for PACs. The sections below describe work that is considered foundational to this research component on unifying the pharmaceutical industry towards common positions that would lead to standardised solutions further in the research.

7.1.1 Pharmaceutical Industry Call to Action

As discussed in Chapter One of this thesis, in October 2016, the researcher established PDA's PAC iAM[SM] Task Force and issued a Call to Action (Ramnarine and Vinther, 2016), inviting the pharmaceutical and regulatory community to come together in tackling the 'wicked problem' of drug shortages. The specific focus of this Call to Action was on overcoming barriers to post-approval control and maintenance of operations, continual improvement and innovation. This marked the beginning of the researcher's work in bringing the pharmaceutical industry together into an awareness, exploration and engagement-raising dialogue on this topic. The objectives of the PAC iAM[SM] Task Force included the following:

- Bring awareness to current challenges, accelerate the dialogue and enable stronger collaboration amongst opinion leaders and key stakeholders (within the pharmaceutical industry, regulatory agencies, and other relevant stakeholders)
- Foster a science and risk-based approach to PAC management and regulatory decision-making for global product quality, safety, and efficacy assessments
- Encourage international convergence or standardisation in PAC management in a manner that can foster and enable mutual reliance between regulatory authorities
- Manage more PACs through the use of an effective PQS without prior regulatory approval

The Call to Action emphasized the important role that the pharmaceutical industry must play in bringing about a reform for PAC management, whereby the global implementation timeline for a PAC can be reduced from years to months. This was identified as an essential factor that would incentivise pharmaceutical companies to innovate and continually improve, thereby contributing to improving the availability of medicines.

The Task Force discussed the importance of developing practical science and risk-based solutions, including a library of PAC examples, and how application of science and risk-based approaches could enable better decisions in determining the submission and approval categories for changes. In addition to developing the solutions and PAC examples, it was also recognised that they should be standardised in order to truly gain

value from them. The Call to Action was also a call to the pharmaceutical industry to come together as one. The expectation was that developing conceptual aspects into practical real-life implementation examples would bring the industry and regulators to a more common and aligned understanding of the mutual challenges and opportunities to collaboratively improve the current state.

7.1.2 Post-Approval Change Innovation for Availability of Medicines (PAC iAM^{SM}) Survey: Is the Regulatory Environment Hindering Much-Needed Innovation in the Pharma Industry?

In 2016, the researcher led the PDA PAC iAM^{SM} Task Force to collect information and data on PAC management experiences from across the pharmaceutical industry, in order to determine the extent of the challenge with global PAC management, and the contributions of the global regulatory complexity towards hindering continual improvement and innovation. This information was collected by means of a survey; the researcher led the design of the survey and it was distributed by PDA to its members as described below. The results of the survey were analysed by the researcher, published in early 2017 (Ramnarine, Busse, Colao, Edwards, Follman, *et al.*, 2017), and were used as a trigger by the Task Force to start expanding awareness and initiating dialogue within the pharmaceutical industry. Simultaneously, while the survey was being carried out, the Expert Working Group that had been convened by ICH to develop ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management,* was in the early stages of developing that new guideline.

PAC iAM^{SM} Survey Design

The survey was designed to explore specific aspects related to the volume of PACs initiated, why PACs were needed, their submission and approval timelines, any impacts on shortages, innovation and burden. Up until that point, the information related to PAC management complexity and burden was mainly anecdotal and perception-based, and the survey was designed to generate qualitative verifiable evidence. The results of the survey presented below confirmed the perceptions and the unintended implications of the global regulatory complexity associated with PAC management, potentially resulting in drug shortages.

To ensure anonymity, the survey was distributed via survey monkey by PDA to all companies that had members in PDA. The results were also collected by PDA.

Survey Results

There were 85 respondents to the survey from Quality, Regulatory, Manufacturing, Technical Operations and Development functions, from Biologics, Small Molecules, Drug Substance and Drug Product manufacturing companies, both generics and innovator companies. 51% of the companies marketed greater than 20 products, and 33% marketed greater than 100 products. 38% of respondents reported that they managed greater than 1000 PACs annually, and 32% reported 50-500 PACs in a year. This was a significant volume of PACs going through the global regulatory system. Almost 40% of companies responded that more than 50% of their changes required submission to regulatory authorities in 25 to 100+ countries, and the changes were not permitted to be managed only within the company's PQS. The survey also explored the reasons for the PACs and found that many of the changes sought by pharmaceutical companies were intended to improve processes (89%), drive innovation (60%) and upgrade aging equipment (71%), with many changes considered major or moderate, and therefore requiring prior-approval.

Respondents almost unanimously (97%) identified the complexity of global regulations as inhibiting both innovation and technological progress. 76% reported that they experienced supply disruptions and drug shortages due to prolonged regulatory approval timelines. Additionally, 65% of companies indicated that they had non-compliance with product registrations because the current knowledge on a product was not represented in the product file. In particular it was of concern to the researcher that 87% of participants reported that they did not proceed with changes due to the regulatory burden. The survey supported the hypothesis proposed by the researcher that:

> *global regulatory complexity contributes to the increased burden of PAC management, increases the barrier for innovation and continual improvement, and could eventually contribute to drug shortages and supply issues.*

Impact of the Survey

The researcher presented the PAC iAM^{SM} survey results at PDA conferences and workshops in 2017-2018 so that it could be discussed by stakeholders. Arising out of these discussions, an infographic (Figure 7.1) depicting the complexity of PACs was

developed by the researcher and Vinther, where approval of every PAC by each regulatory authority was compared to an analogy where every passenger must inspect a plane before it takes off (Stauffer, Vinther and Ramnarine, 2017). Obviously, this is not the case in the aviation industry, but one ponders:

> *'if passengers can trust a system that checks all relevant aspects before a plane's take-off, why could pharmaceutical regulatory authorities not trust pharmaceutical companies to manage moderate or minor PACs within the company's PQS, without requiring a submission and in several instances, a prior-approval by each regulatory authority?'*

Furthermore, is it possible that all regulatory authorities could employ a consistent checklist for PAC assessments, which would lead to a situation where, if one regulatory authority were to approve and confirm acceptance of a PAC, other regulatory authorities could accept this approval, without requiring their own independent review and approval? Four years later, this is now being taken up by ICMRA as part of their strategic PQKMS Initiative, where one of the envisioned capabilities is:

> *"Enabling more extensive mutual reliance among regulators through work to harmonize specific data expectations for sponsors and* ***standards for review among regulators****, so that regulators can be assured of the comparability of the assessments and related determinations of other regulatory authorities on whom they intend to rely."* (ICMRA, 2021)

Figure 7.1: Analogy between PAC Approval and an Airplane Check Prior to Take Off (Stauffer, Vinther and Ramnarine, 2017)

7.1.3 PDA PAC iAM^{SM} Workshop, September 2017

In September 2017, the PDA PAC iAM^{SM} Task Force organised its first 2-day workshop in Washington D.C. Chaired by Ursula Busse, Novartis, and Lisa Skeens, Pfizer, with the researcher a member of the Workshop Planning Committee. The workshop provided insights into several international initiatives such as ICH Q12, touched on practical aspects of PAC implementation, and provided an overview of the PDA PAC iAM^{SM} Task Force's work. There was extensive discussion on the lack of a harmonised global regulatory framework for PACs and how this led to supply chain complexity, slowed down the pace of manufacturing innovation, and increased the risk of quality failures. Several global initiatives to address the issue had been launched by ICH and WHO. Co-sponsored by IFPMA, a trade association operating at a global scale and PDA, this workshop was attended by 80 participants, and featured active participation by speakers and panelists from the FDA, the ICH Q12 EWG, IFPMA, PDA and the pharmaceutical industry.

The workshop provided the case for change, why a global dialogue was essential, what changes were needed, and it presented some proposed global solutions that were being informally discussed by the pharmaceutical industry and regulators. It reflected the most current thinking on the concepts and tools proposed to facilitate PACs and spur manufacturing innovation, through the in-progress ICH Q12 document and beyond.

The researcher made the case through her presentation that much attention had been given thus far to the development & technology transfer phases and less so to the commercial phase of a product's lifecycle. The commercial phase is where companies continued to gain extensive product and process knowledge that needs to be captured in a structured way, making lifecycle management quite dynamic. The researcher provided insights into why KM and QRM must be an integral part of the product lifecycle. She laid out the importance of having a lifecycle management strategy that would be holistic, proactive and global, and she described how an overall product lifecycle could be managed within the company's PQS to ensure that all quality requirements were implemented and maintained according to relevant global and regional regulatory requirements or commitments. The elements of the lifecycle management strategy as described in the PDA Points to Consider Paper, *Technical Product Lifecycle*

Management: Pharmaceutical Quality System Effectiveness for Managing Post-approval Changes (Ramnarine, Busse, Colao, Edwards, O'Donnell, *et al.*, 2017), were also presented by the researcher, along with practical examples of product lifecycle management (PLCM) from Roche, how the company handled this plan within their PQS to manage the lifecycle of a product, and how the plan was used to determine which PACs needed to be filed with regulatory authorities. The researcher emphasized that:

1. A lifecycle management strategy could enable a MAH to manage a product holistically, prospectively and globally, to accomplish the objectives of ICH Q10
2. An effective PQS was essential for establishing and executing the lifecycle management strategy
3. The lifecycle management strategy could serve as an excellent communication mechanism to proactively engage regulatory authorities and build trust
4. A knowledge and risk-based approach could expedite review and implementation of planned PACs, and
5. Proactive and timely exchange of knowledge between pharmaceutical companies and regulatory agencies could reduce PAC notification requirements.

At the workshop, presentations were complemented by interactive case studies, where participants explored concepts and tools proposed by ICH Q12 to better manage PACs, by applying the science- and risk-based approaches mentioned by the speakers. Participants clearly prioritised knowledge management and quality risk management in their change management system to gain regulatory flexibility, as shown in Figure 7.2 which was compiled from a mentimeter[5] pulse survey conducted at the workshop.

[5] An interactive, live polling tool to get real-time input from an audience

Figure 7.2: Mentimeter Pulse Survey on Knowledge Management and QRM as Key to Enable Regulatory Flexibility

The workshop was highly interactive and showed how ICH Q12 could increase opportunities to make changes without prior-approval for the benefit of both the pharmaceutical industry and regulators, if appropriately implemented. It affirmed that companies should work together to develop and implement solutions; additionally, the pharmaceutical industry should work in a transparent and proactive manner with regulators to build trust. Investment in product lifecycle management and PQS effectiveness should be incentivised. All global efforts combined could foster regulatory convergence of PAC regulations, encourage adoption of shared principles, and facilitate continual improvement to spur manufacturing innovation globally.

Towards the end of the workshop, participants shared their views on the impact they anticipated of the current initiatives with ICH Q12 and WHO on PAC management. In general, the views about the impact of these initiative on the current situation did not change from when they were polled on the same question at the beginning of the workshop - 75% still pointed to a favourable impact, while 25% felt that PAC management would just be different as a result of these initiatives. It was acknowledged that, while ICH Q12 would help with some improvements, it would not solve the issue in non-ICH countries which was where global pharmaceutical companies faced the majority of their PAC challenges. Participants also highlighted additional critical success factors for these initiatives - trust, harmonisation, dialogue, courage and practical examples, as shown in the mentimeter results of Figure 7.3. There emerged

evidence of a desire to support standardisation across the pharmaceutical industry and the implementation of shared principles through practical application PAC examples.

Figure 7.3: Mentimeter Pulse Survey on What is Needed in Addition to ICH Q12 and WHO Efforts

The workshop discussions identified the strong link between an effective PQS and successful product lifecycle management. Particular focus on risk-based change management emerged as an area to delve further into, with real-life PAC examples. Overall, the workshop discussions suggested that companies could gain regulatory flexibility in PAC management if they applied the principles of ICH Q8 – 11. A sound scientific understanding of products and processes, coupled with consistent application of QRM, which are embedded in an effective PQS, would provide the basis for ICH Q12 realisation.

The next section describes the two PDA Points to Consider Papers on Product Lifecycle Management that resulted from the PDA PAC iAM^{SM} Task Force's work, with the researcher being the lead author.

7.1.4 PDA Points to Consider Papers on Product Lifecycle Management

The discussions and activities of the PDA PAC iAM^{SM} Task Force were published in two Points to Consider Papers on Technical Product Lifecycle Management, one related to communication and knowledge exchange between Marketing Authorisation Holders

and regulatory authorities (Ramnarine, Busse, Colao, Edwards, Jornitz, *et al.*, 2017), and the other on use of an effective PQS for management of PACs (Ramnarine, Busse, Colao, Edwards, O'Donnell, *et al.*, 2017). The researcher and Vinther co-led the development and authorship of both. The work undertaken in their development resulted in text that was also provided as input to the ICH Q12 Expert Working Group (EWG) for consideration during the drafting of ICH Q12.

The prior work described above by the researcher led to the development of a formal research study, which is the focus of this PhD.

7.2 Research Focus: Making a Case for Change with Chief Quality Officers (CQOs), Sept. 2018

The PAC iAM^{SM} Task Force had started as a small team comprised mainly of volunteers interested in and passionate about improving PAC management. It was becoming evident to the researcher and Vinther, especially given the feedback from Dr Woodcock and senior FDA leaders that, the effort needed to be broadened beyond PDA to the industry level. It also was becoming increasingly important to expand beyond volunteers from companies to ownership by senior leaders that were directly responsible for PAC management and the PQS within their companies. Therefore, in August 2018, the researcher and Vinther along with the PAC iAM^{SM} Task Force members hosted a workshop where attendees were expanded beyond the Task Force to QMS Heads and operational Quality and Regulatory Affairs leaders who were directly involved in PAC management. This workshop became a seeding point for a unified Quality voice on the topic, and an outcome was that the researcher and Vinther seek endorsement to formally establish a single voice of Quality for PAC management.

The CQOs are the senior-most Quality leaders in pharmaceutical companies. The CQOs of the 25 top global pharmaceutical companies regularly meet, at least biannually, for roundtable discussion on Quality hot topics, organised by PricewaterhouseCoopers (PwC). This is a closed forum and no agendas or minutes are published from these sessions due to the nature of confidential company specific information that might come up. After the August 2018 workshop, which is considered as the first *1VQ for PAC* workshop, the researcher and their co-lead met with the CQOs to gauge their interest

and to seek sponsorship from these senior-most Quality leaders for a *1VQ for PAC Initiative*. This meeting took place in September 2018 in Washington DC, and the discussion was framed by the researcher and Vinther as:

> *"How can One-Voice-Of-Quality foster an environment of continual improvement while reducing risk to patient?"*

The discussion focused on elevating awareness by the CQOs of the global PAC complexity, which creates a paradox in which continual improvement is desired and expected, yet it can take years to implement new knowledge into operations.

The CQOs were asked for their level of interest in speaking with one voice to align and standardise the pharmaceutical industry on a standard, risk-based approach for PACs, and to define what constitutes an effective PQS for PAC management. Both aspects could be designed to reduce the number of PACs that were submitted for prior-approval, with more PACs being managed within the PQS only. Development of practical examples as a means to activate the dialogue within the pharmaceutical industry and between the pharmaceutical industry and its regulators was also proposed. The CQOs discussed the importance of finding the right mechanism to present this problem to regulators, including 'what's in it' for regulatory agencies individually, as well as collectively, and ultimately for patients. They discussed concerns that regulators might as a result of this initiative, add more requirements on companies for the documentation of PACs that would be proposed as no longer needing a prior-approval submission. The importance of enabling a culture of trust and transparency with regulators emerged.

The meeting with the CQOs was highly productive, with evidence of a keen interest in the topic demonstrated. They appreciated and acknowledged that the regulatory complexity for PACs slowed down continual improvement and innovation, to a point where it caused additional burden for companies in terms of cost and supply. This was a significant global problem in their view, and in several cases, could lead to supply disruptions. Outcomes of the discussion with the CQOs were summarised as follows and circulated to the attendees (with a request for an update at their next meeting in April 2019):

- Agreement that the current regulatory complexity was increasing with time, and that a concerted effort would be needed to reduce that complexity and allow for more improvement and innovation
- Agreement that this is a 'wicked problem' i.e., highly resistant to solutions
- Endorsement by CQOs of the *One-Voice-of-Quality (1VQ) for PAC Initiative* and agreement to speak with a unified voice
- Agreement that more PACs should be managed within the PQS only rather than requiring prior-approval by regulatory authorities prior to implementation
- Agreement to the development of standard and practical solutions with real examples for:
    - Effective PAC management within the PQS
    - Structured risk-based approach for PACs
- Agreement to assign a representative from their respective companies to be members of the *1VQ for PAC Initiative*
- Agreement to provide specific PAC examples that could be covered solely within the PQS without requiring prior-approval submissions

All subsequent *1VQ for PAC* activities and focus groups were conducted within the context of this high-level framing endorsed by the CQOs.

7.3 *1VQ for PAC* Focus Group Sessions Summary

The research methodology used to bring the pharmaceutical industry together for Part Four of this study was through face-to-face and/or virtual (during the COVID-19 pandemic) focus group sessions, hosted at different pharmaceutical companies that are members of the *1VQ for PAC Initiative* or at the PDA headquarters. The scope of work that was decided on for the *1VQ for PAC Initiative* and Focus Groups at the first session in August 2018, which was subsequently endorsed in September 2018 by the CQOs sponsoring the initiative included:

- Raise awareness of global PAC complexity
- Influence through practical solutions:
    - Elevation of the risk appetite for innovation
    - Management of more PACs within the PQS only – provide specific examples

- Align & standardise the industry on:
    - What is an effective PQS for PACs?
        - Metrics and attributes capable of distinguishing effective vs ineffective PQS for PACs
        - How could it be assessed during inspections?
    - Standard risk-based approach for PACs
- Build a culture of transparency & trust with regulators

Figure 7.4 below lists the *1VQ for PAC Initiative* member companies that have participated in one or more of the focus group sessions and/or CQO Forum discussions.

Figure 7.4: 1VQ for PAC Initiative Member Companies

Eight focus group sessions ranging from one to two-and-a-half days in duration, co-led by the researcher and Vinther, were held between August 2018 through March 2021, with representatives from *1VQ for PAC Initiative* member companies. (Note: *1VQ for PAC Initiative activities* and workshops will continue with the member companies even after completion of this research study). Following the September 2018 meeting (described in section 7.2), where the CQOs confirmed their sponsorship of the *1VQ for PAC Initiative*, an additional eleven focus group sessions were held by the researcher and Vinther with the CQOs sponsoring the initiative and the QMS Heads from these companies. An overview of the format and approach used to conduct these focus groups and review of resulting outputs is provided earlier in Chapter Three, section, 3.5 of this

thesis. A summary of these focus group sessions is provided in Tables 7.1 and 7.2 below.

Table 7.1: Summary of Focus Group Sessions with 1VQ for PAC Member Companies

Focus Group #	Date/Location	*1VQ for PAC* Member Companies	Key Outcomes
1	27-August-2018 PDA, Bethesda	Amgen, Astellas, Biogen, Catalent, Emergent Biosolutions, Intarcia, Johnson & Johnson, Merck, Novartis, Roche/Genentech, Sanofi/Sanofi Pasteur	• Decision to create 1VQ on the importance of implementing new knowledge to continually improve/innovate faster • Decision to take practical actions to improve handling PACs, by standardising the approach across industry • Agreement that the participants would raise awareness about the unsustainable situation with PACs; generate more dialogue with regulators as a single Quality voice • Agreement to define key elements of an effective PQS for PACs and drive implementation within companies – the importance of being consistent across the pharmaceutical industry was acknowledged • Agreement to define, in consultation with regulators, attributes or measures capable of distinguishing effective vs. ineffective PQS for PACs, and discussions with regulators for input and alignment • Agreement to develop a standard risk-based approach for PACs, which would be applied consistently across the pharmaceutical industry • Agreement to assess how to engage with PIC/S to pilot the standard risk-based approach for PACs, with a view to agreeing on what an effective PQS for PACs could look like, and how it could be assessed during inspections • Obtained endorsement from 1st CQO discussion 27-Sept-2018 (DC)
2	13-November-2018 PDA, Bethesda	Amgen, Astellas, Astrazeneca, Bayer, Biogen, Eli Lilly, Emergent Biosolutions, GSK Vaccines, Intarcia, Johnson & Johnson, Merck, Novartis, Novonordisk, Roche/Genentech, Sanofi/Sanofi Pasteur	• Agreement on the ambition - at least 50% reduction of prior-approval PACs by end 2021 • Agreement on attributes to demonstrate effectiveness of PQS for PACs ***Foundational Attributes (across all PACs)*** ○ Company is cGMP compliant ○ Company demonstrates right quality culture (e.g., no recurring issues) ○ Company demonstrates a robust quality risk management programme

Focus Group #	Date/Location	*1VQ for PAC* Member Companies	Key Outcomes
			○ Company resources proactively allocated to continual improvement activities ○ PACs initiated by proactive continual improvement projects (as part of the company's Quality Plan) ○ New knowledge (complaints, operations, Annual Product Review (APR)/ Product Quality Review (PQR), etc.) integrated into PACs ○ Company inspection or audit findings related to management of PACs ***Metrics/Attributes for Individual PACs*** ○ Formal risk management performed for each PAC ○ Adherence to implementation timelines for PAC ○ PAC and CAPA Effectiveness ○ PACs with unintended risk or consequence (deviations) ○ No unacceptable risks introduced as a result of PAC • Agreement to develop 4 specific PAC examples ○ Excipient supplier name or address change - with no change in manufacturing site, equipment, material, process, or material grade or specification ○ Drug product batch size increase – with no change in equipment ○ New technology – rapid microbiology method ○ New technology for indirect product quality testing such as environmental monitoring • Obtained support and sponsorship from QMS Head Forum, 6-Mar-2019 (London)
3	27-March-2019 PDA, Bethesda	Amgen, Astrazeneca, Bayer, Biogen, Catalent, Eli Lilly, Emergent Biosolutions, GSK Vaccines, Intarcia, Johnson & Johnson, Merck, Novonordisk,	• Finalised *1VQ for PAC* Concept Paper • Agreement to deliver the following from the *1VQ for PAC* Concept Paper ○ Define and demonstrate **effectiveness of the PQS** for management of PACs - so that more changes can be managed

Focus Group #	Date/Location	*1VQ for PAC* Member Companies	Key Outcomes
		Roche/Genentech, Sanofi/Sanofi Pasteur	in the PQS or via notification pathways, instead of prior-approvals ○ **Standard risk-based assessment of PACs** incorporating latest product and process knowledge ○ **Pilot** proposed solutions with a limited number of companies. Seek input from regulatory agencies on outcomes • Agreement to develop 3 additional PAC examples ○ Implementation of a new reference standard ○ Extension of DP shelf life ○ Compendial changes • Agreement to develop general PAC framework for a new technology implementation (as a notification instead of prior-approval submission**)** • Obtained endorsement for Concept Paper at 2nd CQO Forum, 4-Apr-2019
4	19-20-Jun-2019 GSK, Rockville	Amgen, Astrazeneca, Biogen, Eli Lilly, Emergent Biosolutions, GSK Vaccines, Intarcia, Johnson & Johnson, Merck, Novartis, Roche/Genentech, Sanofi/Sanofi Pasteur	• Established sub-teams to work on the deliverables ○ Sub-team 1: Effectively Managing PACs in the PQS ○ Sub-team 2: Standard Risk-based approach for individual PACs • Decided on specific outputs for each sub-team ○ Sub-team 1: A document that would be written at the level and format of ICH Q10 and ICH Q12 describing the 'what' and not the 'how' for effective management of PACs in the PQS. The team determined that it would be written as though it could be an Annex 3 to ICH Q10, specifying what should be in the PQS to effectively manage PACs (especially for changes that could be downgraded from prior-approval submissions) ○ Sub-team 2: A document that would describe a standard risk-based approach to manage individual PACs (applying ICH Q9 and Q12 principles) • Developed standard template for PAC examples

Focus Group #	Date/Location	*1VQ for PAC* Member Companies	Key Outcomes
			• Decided on highlights for next updates to CQO Forum 19-Sept-2019, and QMS Heads Forum 24-25-Sept-2019
5	15-16-October-2019 Biogen, Raleigh	Amgen, Astrazeneca, Biogen, Eli Lilly, Emergent Biosolutions, GSK Vaccines, Intarcia, Johnson & Johnson, Merck, Novartis, Roche/Genentech, Sanofi/Sanofi Pasteur	• Finalised solutions from sub-teams 1 and 2 for Effective PQS for PACs and Risk-Based Change Management • Initiated Communication & Implementation Planning • Continued development of PAC examples

6	26-27-February-2020
	Merck, Philadelphia
		Amgen, Astrazeneca, Biogen, Catalent, CSL Behring, Eli Lilly, Emergent Biosolutions, GSK Vaccines, Intarcia, Johnson & Johnson, Merck, Roche/Genentech, Sanofi/Sanofi Pasteur, PDA	• Finalised *1VQ for PAC* Solution paper – Effective PQS for PACs including risk-based decision tree
			• Developed *1VQ for PAC* Implementation Plan outline for
			  ○ PIC/S Recommendation Paper
			  ○ *1VQ for PAC* Solution Paper
			  ○ *1VQ for PAC* Examples
			• Continued development of *1VQ for PAC* Communication Plan
			• Agreement to develop *1VQ for PAC* position papers for the following PAC examples
			  ○ Automated colony counter
			  ○ Drug product scale change
			  ○ Compendial excipient update
			  ○ Drug product shelf-life change
			  ○ Analytical instrument model change
			  ○ Reference standard update
			  ○ Analytical new technology

7	30-31-July-2020 Virtual	Amgen, Astrazeneca, Biogen, Catalent, CSL Behring, Emergent Biosolutions, GSK Vaccines, Intarcia, Johnson & Johnson, Merck, Novartis, Roche/Genentech,	• Discussed COVID-19 impact and experiences and what to retain post-pandemic • Further development of Management Review *1VQ for PAC* position paper • Refinement of the *1VQ for PAC* message to continue increasing awareness of the problem and expand involvement from companies and

Focus Group #	Date/Location	*1VQ for PAC* Member Companies	Key Outcomes
		Sanofi/Sanofi Pasteur, PDA	regulatory authorities that had not yet engaged in the effort • Agreement that all companies would complete a maturity assessment against the PIC/S Recommendation Paper *How to Evaluate/Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management* • Development of a standard approach to assess maturity gaps against the published draft PIC/S Recommendation Paper
8	29-30-March-2021 Virtual	ADMA Bio, Amgen, Astrazeneca, Biogen, Catalent, CSL Behring, Emergent Biosolutions, GSK Vaccines, Intarcia, Johnson & Johnson, Merck, Novartis, Roche/Genentech, Sanofi/Sanofi Pasteur, PDA	• Aligned on 2021 objectives & key activities including publications (see section 7.4) • Refined *1VQ for PAC* messaging and communication deck • Discussed status of PAC examples in progress and agreed on next PAC examples • Dialogue on implementation of ICH Q12 and *1VQ for PAC* solutions within companies

Table 7.2: Summary of Focus Group Sessions with 1VQ for PAC Sponsoring CQOs and QMS Heads

Date	Focus Group Attendees	Key Outcomes

March-2019	QMS Heads Focus Group Session #1	• Awareness of wicked problem of continual improvement, innovation and drug shortages. The significance of the problem and the need for practical solutions was confirmed.
		• Provided update on decision from CQOs of 25+ global pharma companies to sponsor the *1VQ for PAC Initiative*
		• Obtained commitment from QMS Heads for the *1VQ for PAC Initiative* and to implement resulting solutions within their companies for the following:
		  ○ How to demonstrate effective management of PACs in the PQS so that more changes can be managed in the PQS or via notification pathways, instead of prior-approvals
		  ○ How to perform standard risk-based assessment of individual PACs that incorporates latest product and process knowledge
		• QMS Heads committed to partnering with Regulatory Affairs Heads within their respective company to realise the vision of ICH Q9, Q10 and Q12
		• QMS Heads committed to share approaches and examples from their companies on how to demonstrate an effective PQS to reduce regulatory burden for PACs

April-2019	CQOs Focus Group Session #1,	• CQOs discussed the wicked problem of continual improvement, innovation and drug shortages as a follow up to their September 2018 meeting. The significance of the problem and the need for practical solutions was confirmed.
		• Appreciated the terminology 'wicked problem' as it is indeed 'highly resistant to solutions'
		• CQOs agreed to sponsor the *1VQ for PAC* Concept Paper and approved it with the following. Published paper incorporated these edits
		  ○ Add text regarding regulatory agencies already having company specific information indicating the effectiveness of a PQS such as inspection reports, PACMPs, and various reports and information exchanged between the agency and the company
		  ○ Add text specific to state that downgrading a change from prior-approval can either be notification or annual report

Date	Focus Group Attendees	Key Outcomes
		• CQOs were pleased with progress and agreed to continue their support and allocate senior level resources from their companies • Asked that dialogue should continue with regulatory agencies across the world and with PIC/S • Asked team to consider more data that objectively shows the magnitude of the problem in a way that can be used in a tangible, constructive way. Examples - like 8,000 prior-approval submissions in one year from one company, > 99 % of changes approved, 80 % of RA team working on PACs • Discussed that PAC assessments generate significant revenue for regulatory agencies. Reducing PACs requiring prior-approval would reduce this revenue. Potential to consider an alternative fee structure where individual PAC assessments aren't revenue drivers. • Encouraged expansion of the initiative to more companies including CDMOs • Supported develop of practical PAC examples that should be downgraded from prior-approval to notification or annual report. But asked to be cautious not to generate more reporting or complexity • Asked how CQOs could play a role in advancing this topic. Public and company internal support both were noted as essential.
September-2019	CQOs Focus Group Session #2	• CQOs continued to strongly sponsor and support the 1VQ on PAC Initiative ("We are all in") • Pleased that the CQO-endorsed *1VQ for PAC* Concept Paper was published, as well as the progress on the Effective PQS, Risk-Based approach solutions (decision tree) and PAC examples. Asked for development of more PAC examples. • Informed of the PIC/S Recommendation Paper and its expectations • Appreciated the importance of speaking with One Voice and standardised approach to PAC management across the industry • Asked researcher for communication materials to share within their companies • Discussed the paradox of regulatory agencies expecting innovation and continual improvement on the one hand and having rigid regulatory framework that doesn't apply a science and risk-based approach on the other hand
September-2019	QMS Heads Focus Group	• Asked researcher for a common storyboard and case for change as communication

Date	Focus Group Attendees	Key Outcomes
	Session #2	material • Discussed value gain from science and risk-based approach to PAC management • Developed a common implementation plan framing to be used by all companies • Discussed opportunities to pilot solutions within companies • Discussed influencing plan, targeting conferences attended by regulators too • Discussed importance of involving Regulatory Affairs within companies for implementation • Agreed on the need to get input from both reviewers and inspectors on the *1VQ for PAC* solutions and PAC examples • Discussed how to influence solutions and examples being included in the ICH Q12 training package • Aligned on the industry position paper approach for simple PACs that could be downgraded • Discussed PAC examples that should be downgraded
March-2020	QMS Heads Focus Group Session #3	• Aligned that no pilot was needed for *1VQ for PAC* solutions. Companies would simply implement the published *1VQ for PAC* examples position papers • Acknowledged the need to continue to raise awareness of the global complexity • Many companies informed that they had initiated exchange between their Quality and Regulatory Affairs functions for implementation • Emphasized the need for a joint meeting between CQOs and Regulatory Affairs Heads • Action: Continued PIC/S engagement; engage reviewers on published *1VQ for PAC* • Additional request made by researcher to QMS Heads: o Raise awareness and advocacy for *1VQ for PAC* through their interactions o Drive implementation of *1VQ for PAC* solutions in their companies o Provide input on *1VQ for PAC* communication messages o Provide PAC examples that are currently prior-approval, but should not be
April-2020	CQOs Focus Group Session #3	• Continued strong sponsorship and willingness from CQOs to show public support for *1VQ for PAC* o CQOs agreed to have their names and their companies added as endorsing companies to *1VQ for PAC* publications o Asked that the *1VQ for PAC* solutions paper be made stronger and relevant for

Date	Focus Group Attendees	Key Outcomes

		COVID-19 challenges
		• Agreed that meeting with FDA (CDER, CBER) along with Regulatory Heads would be useful. Asked that other regulatory authorities be invited
		  ○ Followed-up with FDA and other regulatory authorities was that such a meeting would be challenging to organise due to pandemic priorities
		• Agreed to a joint CQO-Regulatory Heads
		• Additional requests made to CQOs:
		  ○ Support implementation of *1VQ for PAC* solutions in their companies
		  ○ Provide input on *1VQ for PAC* communication messages
		  ○ Provide PAC examples that are currently prior-approval, but should not be

September-2020	QMS Head Focus Group Session #4	• Key communication messages were discussed • Reviewed and sought feedback on the 1VQ Management Review checklist position paper • Sought support to complete the PIC/S Recommendation Paper maturity assessment for their companies • Sought feedback on communication slides and key *1VQ for PAC* messages • Updates shared on *1VQ for PAC* activities and deliverables
September-2020	CQOs Focus Group Session #4	• CQOs continued to sponsor the *1VQ for PAC Initiative*; emphasized the CQOs role regarding regulatory flexibility solutions • Continued raising awareness about 1) the PAC complexity and 2) the CQOs solution to manage more PACs in the PQS only • Key communication messages were discussed; recommended adding communications experts • Updated the communication slides and further clarified the messages • Agreed to a joint focus group session between CQOs and Heads of Regulatory Affairs • Reviewed and provided feedback on the 1VQ Management Review checklist position paper • Agreed to complete the PIC/S Recommendation Paper maturity assessment for their companies
November-2020	CQOs and Regulatory Heads Joint session	• First joint session between the senior-most leaders for Quality and Regulatory Affairs within companies

Date	Focus Group Attendees	Key Outcomes
		• Quality and Regulatory Heads aligned on the objectives and scope of *1VQ for PAC Initiative* • Agreed to work together on 1) implementation in their respective companies and 2) outreach to regulators • Discussed that biggest challenge with global regulatory complexity comes from non-ICH countries; agreed to leverage Regulatory functions in country Affiliates and influence through WHO too • Agreed on the importance of continuing to raise awareness of this wicked problem and emphasising the science and risk-based approach • Discussed learnings and improvements from COVID-19 that should be retained post pandemic e.g., electronic documents • Asked for communication material for companies to engage Affiliate Regulatory functions
March-2021	CQOs Focus Group Session #5	• CQOs continues to actively sponsor the 1VQ on PAC Initiative and were happy with progress • CQOs supported having a workshop with FDA (and potentially other agencies) once feasible • The objectives of *1VQ for PAC Initiative* for 2021 were agreed to (as described in section 7.4). It was suggested to engage more agencies like China, Russia and non-ICH countries. CQOs agreed to provide their top 3-5 countries to engage with • Agreed to establish a small *1VQ on PAC Initiative* governance group with the researcher, co-lead and 2-3 CQOs • Provided a draft for input from CQOs on the roles of the QMS Heads and the CMC RA Heads in context of transforming PAC management. • Clarified the specific role of the CQOs in driving simplification of the PAC complexity by offering the *1VQ for PAC* solutions to manage more PACs in the PQS only
March-2021	CQOs Focus Group Session with Dr Theresa Mullin (CDER)	• First direct session organised by researcher and Vinther between CQOs and Dr Theresa Mullin, FDA • The CQOs shared examples of challenges with the multi-year approvals and global complexity of PACs • Dr Mullin shared her views especially that we are at the beginning of risk-based

Date	Focus Group Attendees	Key Outcomes
		management of PACs • She was very supportive of a system-based global approach to PAC management • She stated that COVID-19 disruption had reinforced the need for change and more regulatory reliance - it would take time though • She shared that FDA and other agencies were working actively on more regulatory reliance. That required better data standards and standardised data sharing through technology solutions • CQOs actively supported more regulatory reliance but reiterated that the pharmaceutical industry's work was mostly related to regulatory flexibility • FDA was interested in doing pilots and examples with the CQO group • CQOs confirmed that in general PACs were the same globally, but the approval timeline and reporting requirements differ from country to country • Discussed that a simplified PAC global framework must keep the patient in mind and at the centre. They stated that one of the lessons learned from the pandemic was more willingness to use a risk-based approach to PAC management • The CQOs also noted the role they have as owners of the PQS and decision makers on all quality matters at the company. Therefore, they asked to be heard more and be involved in PAC simplification work particularly related to defining an effective PQS for managing PACs

In addition to using the focus group sessions as summarised in Tables 7.1 and 7.2 to seek input, gain alignment and secure implementation commitment from the *1VQ for PAC* member companies, the researcher also utilised them as working sessions to design, iterate, influence direction, and finalise practical solutions that are expected to drive meaningful impact and shifts in accelerating continual improvement and innovation in the pharmaceutical industry.

The next section describes the 2021 workplan for the *1VQ for PAC Initiative* that will continue beyond this research.

7.4 2021 *1VQ for PAC* Work Plan

The objectives for 2021, as endorsed by the CQO in March 2021, were centred on demonstrating a real reduction in PAC complexity from the application of the *1VQ for PAC* solutions. This would be accomplished through 3 sub-elements:

- Improve awareness
    - CQOs accountable for PQS and owning 'effective PQS for PAC' solution, including the science & risk-based approach
    - Publish PAC problem & *1VQ for PAC* solution, practical examples
- Increase engagement
    - Workshop and meetings with regulatory authorities and pharmaceutical companies
    - At least one regulatory authority and company *1VQ for PAC* joint pilot
    - Involve more regulatory authorities (e.g., China, Russia, non-ICH countries) and companies
- Enable implementation
    - Initiate implementation of *1VQ for PAC* solutions in companies

The *1VQ for PAC Initiative* aligned on these objectives for 2021, and the member companies reiterated that implementation would require joint collaboration between Quality and Regulatory. It was agreed that company internal training materials for implementation of *1VQ for PAC* solutions would be developed by the companies, and shared within the *1VQ for PAC* community. The next part of this thesis elaborates on the practical solutions resulting from the work described thus far in this thesis.

Part Five: Practical Science and Risk-Based Solutions

Part Five focuses on practical, standard, global solutions that facilitate effective delivery of medicines to patients. These solutions are a result of ongoing collaborative work within the pharmaceutical industry through the *1VQ for PAC Initiative*, with ongoing input from regulators. The solutions are based on the current and latest thinking and concepts on product lifecycle management and PAC management, as laid out in ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (ICH, 2019), and are provided below in Chapter 8.

Chapter Eight

Standard Solutions for the Pharmaceutical Sector

The term 'pharmaceutical sector' is intended to encompass pharmaceutical companies and regulatory authorities, two key stakeholders and contributors to this research study and its outcomes. It also includes academic groups such as the PRST at the Technological University, Dublin, where direct collaborations with the pharmaceutical industry and its regulators have led to patient-focused advancements since its inception in 2005. An overview image of this landscape is provided in Chapter Two, Figure 2.4 of this thesis. Pharmaceutical companies and regulatory authorities are distinct entities with clear separation and independence of roles in relation to serving patients and public health needs. However, they are not mutually exclusive, and there is a definite interconnectedness between them when it comes to the design, implementation and value realisation from solutions resulting from this body of work.

As described in Chapter Seven of this thesis, in response to FDA's suggestion, the researcher, with Vinther, brought the pharmaceutical industry together through the CQO-sponsored *1VQ for PAC Initiative* to develop and propose standard solutions to improve PAC management and advance innovation in the pharmaceutical industry. The body of work undertaken via the *1VQ for PAC Initiative* focus group sessions also formed the basis for bringing in regulators to discuss their perspectives, collect their input, and verify relevant applicability and usefulness of the solutions for regulatory authorities too.

This chapter reviews the *1VQ for PAC* Concept Paper that was developed under the researcher's leadership, and represents the commitment of Senior Quality Leaders as the unified voice of the pharmaceutical industry. It also describes the four resulting solutions and practical application PAC examples that have been published.

8.1 Review of the *1VQ for PAC* Concept Paper - *Solving the Global Continual Improvement and Innovation Challenge: How an Effective Pharmaceutical Quality System Can Transform Post-Approval Change Management*

In the first step towards developing a *1VQ for PAC* Concept Paper, *Solving the Global Continual Improvement and Innovation Challenge: How an Effective Pharmaceutical Quality System Can Transform Post Approval Change Management* (Vinther and Ramnarine, 2019a), the researcher started by reviewing the intent of the original ICH Q10 Concept Paper (ICH, 2005b), approved in November 2005.

The ICH Q10 Concept Paper proposed that the ICH Q10 guideline would provide a framework for a modern and internationally harmonised quality system for pharmaceutical manufacturing that would build upon the cGMPs, and facilitate continual improvement while ensuring product realisation and maintenance of a state of control. In the Concept Paper, the PQS was envisioned as encouraging a *science and risk-based approach* to quality decisions, *facilitating innovation and continual improvement* throughout the product lifecycle. It was envisioned that ICH Q10 would, when implemented, provide a mechanism for assuring that there would be no unintended consequences of continual improvement, and demonstrating commitment from both the pharmaceutical industry and regulators to utilising robust quality systems, activating innovation, and assuring the consistent global availability of medicines (ICH, 2005b).

A review of the Concept Paper and ICH Q10, together with the feedback from FDA discussions presented in Chapter Six of this thesis reiterated for the researcher that the reason the anticipated benefits had yet to be realised might be because there was no guidance available on what the practical application of utilising the PQS and a science and risk-based approach should entail. There also was no practical definition on how to demonstrate effective management of PACs within the PQS. All of this resulted in, albeit unintended, a high burden of cost, resources and effort for both companies and regulators in implementing improvements and innovation through PACs. This research set about to address these issues, by developing practical guidance, standard solutions

and proposed examples of how to demonstrate effective management of PACs within the PQS.

Hence, the *1VQ for PAC* Concept Paper, utilising the approach, outline, sections and flow similar to ICH Concept Papers, focused on designing and implementing standard solutions for the pharmaceutical industry in these areas. The solutions specifically targeted utilisation of an enhanced science and risk-based approach within the construct of an effective PQS to achieve timely and faster implementation of new knowledge gained and innovation by making PACs. By consistent and global implementation of these solutions it was envisaged pharmaceutical companies would have common standardised ways to demonstrate to regulators that they were utilising the latest product and process knowledge and had a robust PQS to manage changes and continual improvement. The intended outcome was that regulators could trust the concerned companies to manage certain PACs solely within their PQSs without additional regulatory approval.

The *1VQ for PAC* Concept Paper described the perceived problem from a pharmaceutical company's perspective and how this led to a global complexity that impacted product availability for patients. The primary premise was that a company's latest product and process knowledge, and the strength of its PQS, were not factored into the regulatory assessment and decision-making on individual PACs. This meant that even changes that could be well-justified for a simple regulatory notification or management solely within the PQS (based on the change being low risk, and the strength of the PQS in effectively managing such low-risk changes), still had to be submitted to each relevant regulatory authority for prior-approval. This resulted in delayed improvements and innovation, sometimes at the cost of increasing risk to product quality and availability for patients. One example (among others) from the researcher's direct experience is related to replacing visual colony counting test methods (with manual result reporting) with a rapid micro automated colony counter system for routine water monitoring, environmental monitoring and even in-process and drug substance product related testing. The automated method and technology provided shorter assay times, earlier detection of micro colonies over the human eye, faster time to results and reduced review times (counts the same colonies in half the time of the traditional method) that enabled faster response to contamination events, did not impact

the ability to detect slow-growing organisms, improved data integrity with automated and validated result interface with the Lab Information Management System (LIMS), eliminated manual (human) plate counting and manual data entry into LIMS – yet this technology has not been widely implemented across the pharmaceutical industry to the extent it can and should be because of the global PAC complexity of introducing such a change.

The strategic importance of this topic was the implementation of the vision laid out in the ICH Q10 Concept Paper, and as clearly articulated in ICH Q10 Annex 1. The aspiration of the *1VQ for PAC Initiative* was:

> "*increased innovation and faster implementation of new knowledge through a transformational shift in PAC implementation timelines with at least 50% reduction in prior- approval PACs*."

The standard solutions that the *1VQ for PAC* Concept Paper committed to delivering were as follows:

1. Define and demonstrate effective management of PACs in the PQS, so that more changes could be managed within the PQS instead of via prior-approvals
2. Develop a standard risk-based assessment of PACs incorporating the latest product and process knowledge
3. Pilot the proposed solutions

The *1VQ for PAC* Concept Paper was sent to FDA for their feedback which was substantive particularly in relation to industry proposing how to demonstrate effectiveness of the PQS for PAC management, improving evaluation of this PQS effectiveness during inspections, and the need to engage with other regulatory authorities beyond FDA. The researcher and Vinther adjudicated all received FDA comments, accepting most, and revised the Concept Paper accordingly. The revised paper was extensively reviewed by approximately 400+ people across the *1VQ for PAC* member companies, including their PQS/QMS Heads, comments were collated and adjudicated by the researcher and Vinther, before it was finalised and approved by the CQOs. It was published in September 2019 in the peer-reviewed PDA Journal (Vinther and Ramnarine, 2019a).

The subsequent sections in this chapter describe the standard solutions that were developed as per the scope of the approved *1VQ for PAC* Concept Paper.

8.2 Solution 1: Industry *1VQ for PAC* - Effective Management of Post-Approval Changes in the Pharmaceutical Quality System

Through the first two *1VQ for PAC* Focus Group sessions, described in Chapter Seven of this thesis, the specific elements of the PQS that are essential in the proactive and effective management of PACs were identified. The starting point for the PQS discussions were ICH Q10 and the published *PDA Points to Consider* paper, *Technical Product Lifecyle Management: Pharmaceutical Quality System Effectiveness for Managing Post-Approval Changes* (Ramnarine, Busse, Colao, Edwards, O'Donnell, *et al.*, 2017). The focus group discussions also explored attributes and metrics that could demonstrate effective use of the PQS for PAC management. This in turn could allow faster implementation of changes that improve quality, ensure a sustainable supply of medicines and enable innovation, all based on the latest product and process knowledge.

Initially, one might think that the Change Management system might be the only PQS element that is relevant and applicable for PAC management. However, the finding that emerged through the focus groups sessions was that, in addition to change management, there were other proactive and reactive components of the PQS that were important for demonstrating effective management of PACs within the PQS. In fact, it became apparent that the systems framework of the ICH Q10 PQS model, with the four PQS elements (Management Review, PPPQMS, CAPA, and Change Management) and the two enablers (QRM and KM), were all essential for effective management of PACs. This was because:

- Typically, these PQS elements and enablers were the first points to capture the triggers or signals that indicated a change or a corrective or preventive action might be needed
- Then the PQS provided the processes and framework for responding to the triggers, managing the resulting actions
- Finally, the PQS verified them for effectiveness

These interdependencies are depicted in Figures 8.1 which builds upon the ICH Q10 diagram to propose mechanisms to support PAC regulatory filing assessments. Then Figure 8.2 gives details of how this support can be generated, relating it back to PQS. Both figures were developed and published by the researcher in May 2020 (Ramnarine *et al.*, 2020). By applying these, the PQS could help determine the regulatory filing approach for a PAC.

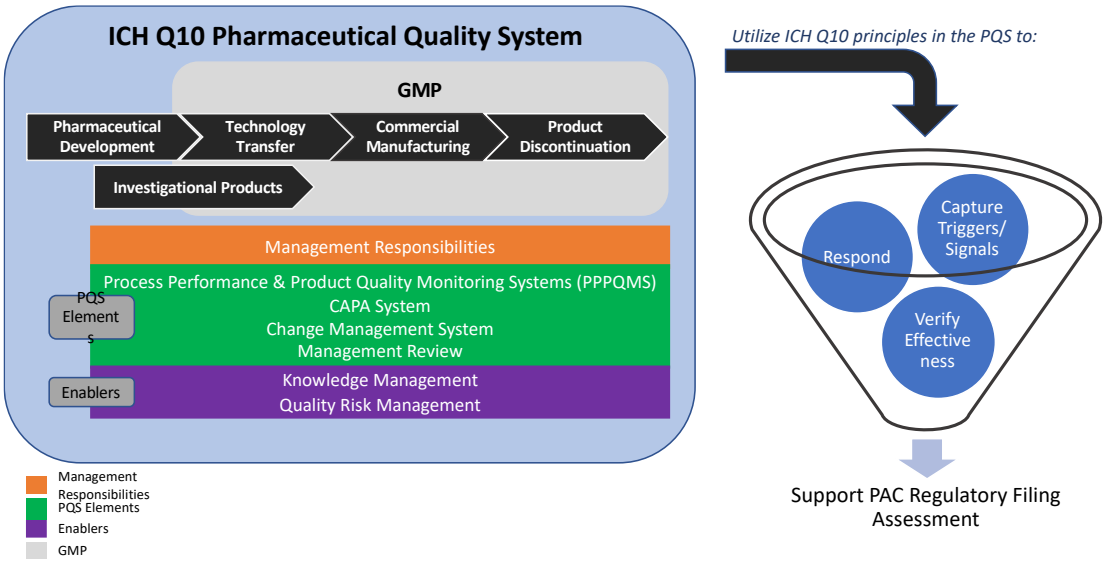

Figure 8.1: Utilising ICH Q10 for Effective Management of PACs (Ramnarine *et al.*, 2020)

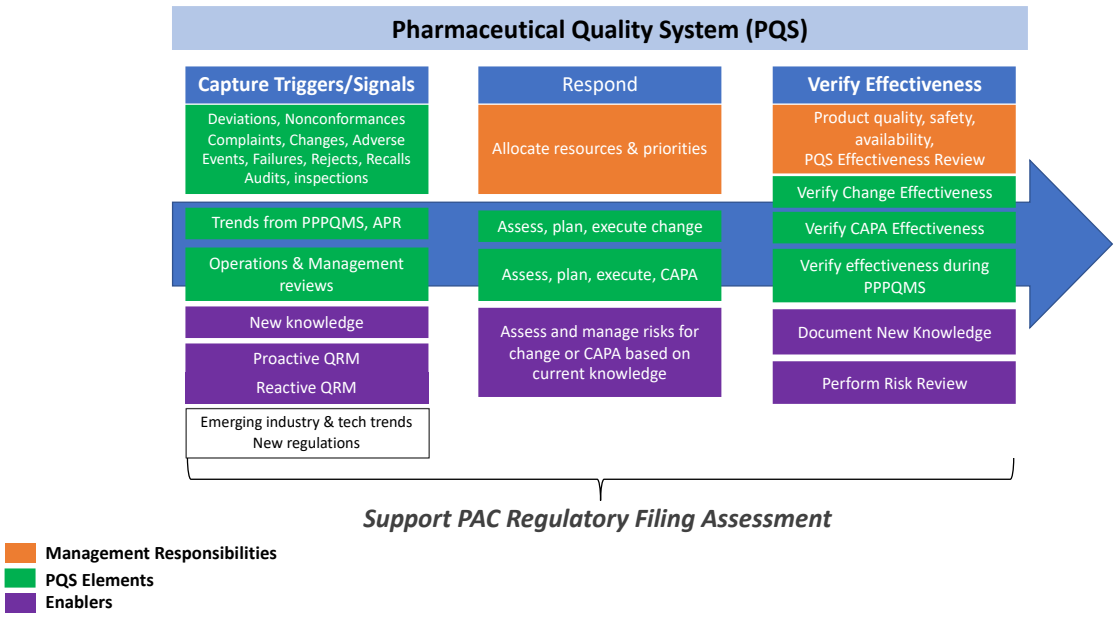

Figure 8.2: Maintaining a State of Control, Facilitating Continual Improvement and Effective Management of PACs in the PQS (Ramnarine *et al.*, 2020)

This *1VQ for PAC* solution (shown in the figures above) described the role of the PQS in extending beyond GMP compliance, and functioning as a holistic system, which if utilised appropriately, could enable regulatory flexibility for faster and more timely PAC management. This solution built on ICH Q10, and further defined specific details on how each of the four PQS elements and the two enablers could be used to demonstrate effective decision-making and management of PACs. It provided specific guidance on practical utilisation of the PQS, which, as highlighted in feedback from FDA and the focus groups, had been missing.

Companies could directly adopt and implement within their current PQS the details for the PQS elements and enablers specifically for PAC management, as defined in this solution. This would not only allow a company to strengthen its PQS, but consistent implementation of this solution could also standardise the pharmaceutical industry. Regulators would then see companies using the same attributes of the PQS to implement PACs faster, and demonstrate that they were able to do this well within the framework of an effective PQS.

8.3 Solution 2: Industry *1VQ for PAC* - Risk-Based Assessment of Individual PACs

While pharmaceutical companies and regulatory authorities have worked tirelessly over the past decade to improve implementation of the principles and concepts of QRM as described in ICH Q9, *Quality Risk Management*, at the time of writing this thesis, the vision of risk-based decision-making has yet to be widely realised in the pharmaceutical environment. The science and data-basis for QRM application and risk-based decision-making considering balanced risk-benefit assessments remains weak, both in the pharmaceutical industry and in regulatory authority processes, as demonstrated by the following:

- Risk assessments are performed by companies, but they are not always updated with the latest product and process knowledge
- Risk-based decisions are made by regulators, but they are typically based on a generic risk understanding, not on the totality of a company's specific product knowledge and its latest risk controls
- Risk-benefit assessments for PACs are not performed well, especially in context of the expected improvements relative to the potential risks they might present and their associated mitigations to further improve the risk-benefit balance
- Additionally, effectiveness of the PQS in identifying and managing risks in a timely manner is not visible to regulators in the right context, and therefore, it is not considered in regulatory decision-making
- Finally, even though the risks remain the same, different decisions are made by regulatory authorities in different countries for the same risks

The result of this weak risk-based application is that decisions are based on potential 'worst-case' or generic risk scenarios, instead of being based on the extent of product and process knowledge that is in place. For example, a regulatory submission to introduce a Process Analytical Technology (PAT) application in order to significantly enhance process monitoring capabilities will usually be assigned the highest level of regulatory assessment possible, e.g., via a Type II variation in the EU, regardless of how much prior knowledge and process understanding the applicant has. The extent of regulatory assessment and questioning that accompanies such applications, regardless of

where the applicant is starting from in terms of process understanding and product knowledge, and the unpredictability as to approval timelines, have led many companies to simply not seek to register their PAT applications at all. The unfortunate net effect of this is that the use of such advanced technologies in product quality decision-making does not get realised, and offline, traditional and older batch monitoring methods remain in place. This hinders continual improvement and innovation, that ultimately results in delayed benefits for patients.

It is the researcher's opinion that the application of an enhanced science and risk-based approach at an individual PAC level is essential if one is to realise the ICH Q10 Annex 1 vision, where more knowledge and better risk controls should enable more regulatory flexibility and faster implementation of PACs.

Science knows no country or regional borders – to quote Dr Louis Pasteur:

> *"Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world. Science is the highest personification of the nation because that nation will remain the first which carries the furthest the works of thought and intelligence."*

A standard science and data-based risk assessment, founded on the latest product and process knowledge, could be expected to enable alignment between a pharmaceutical company and regulators, and among regulators on the categorisation and decision-making for PACs. The researcher contends that an enhanced and fully transparent science and risk-based approach is essential and would also build trust between companies and regulatory authorities. It could accomplish this as follows:

- A pharmaceutical company would perform a risk assessment for a proposed PAC using the latest product & process knowledge; this would be documented in the company's PQS
- The proposed change category would be based on the PAC risk level, the company's proposed risk controls, and the effectiveness of the company's PQS
- The company's PAC risk assessment, based on the latest knowledge, would be made transparent to regulators to enable a *level 1* calibration & alignment between the company and the regulatory assessor on the risk level, change category, and implementation timelines for the PAC; the risk assessments for

any PAC's that were not submitted for prior-approval would also be available for review during inspections

- The company's PAC risk assessment would also enable a *level 2* calibration and alignment between regulatory assessors from different countries on the risk level, change category, and implementation timelines for the PAC

Figure 8.3, developed by the researcher, illustrates on the left-hand side how, in the current state, and regardless of the level of specific product and process knowledge, a PAC is categorised, assessed and handled. The desired future state, depicted on the right-hand side of Figure 8.3, is that the same PAC (e.g., change in a starting raw material that can impact a Critical Quality Attribute (CQA)), could result in different regulator decisions for different companies, based on the level of knowledge, risk and the strength of the company's PQS at each company.

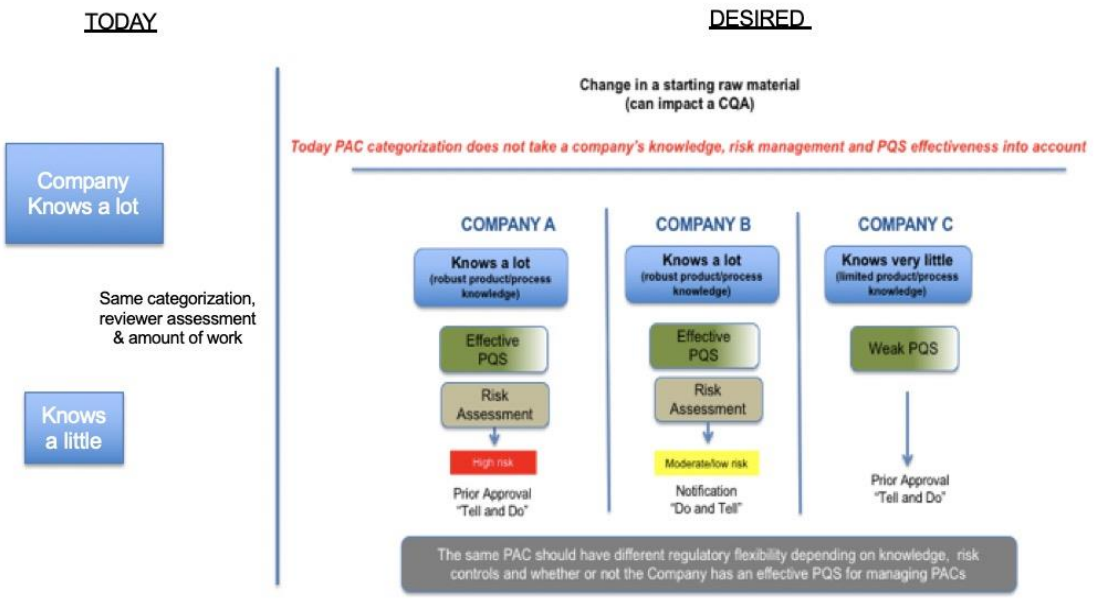

Figure 8.3: Illustrative Example on Utilisation of Knowledge and Risk to Provide Appropriate Flexibility in PAC Management

The researcher noted that there was a difference between basic QRM and an enhanced QRM application, with the latter presenting the possibility of unlocking the regulatory flexibility potential as envisioned in ICH Q10 Annex 1. Figure 8.4, also developed by the researcher, describes the current state for PAC management and the distinction between basic and enhanced QRM application for assessing an individual PAC.

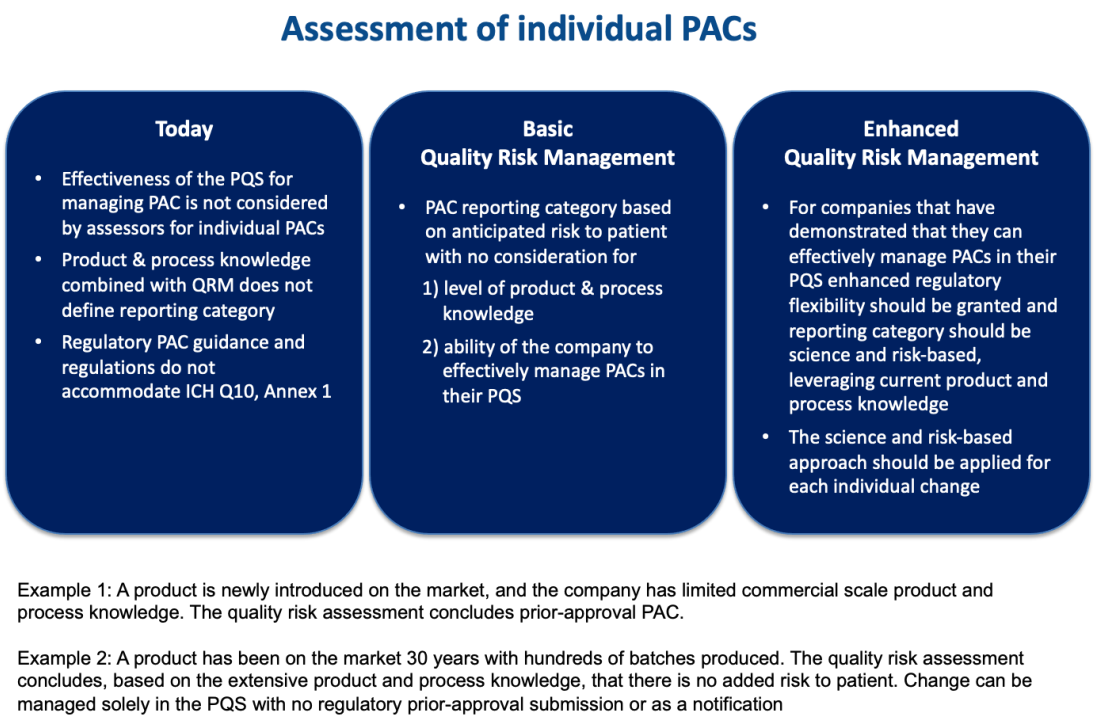

Figure 8.4: Basic vs. Enhanced Risk Management Application for PACs

The objectives for this second *1VQ for PAC* solution were:

- A standard, objective, science and risk-based approach for PAC assessment that utilised the latest and specific product and process knowledge, and
- Facilitating a process whereby the same PAC decision outcomes are made by the company and all relevant regulatory authorities

The approach the researcher facilitated in the focus groups to develop solution 2 was to:

1. Expand on the ICH Q12 decision tree (ICH, 2019) (shown in Figure 8.5), and
2. Integrate the risk-based approach into the change management process

This would allow the PAC categorisation to be based on the company's risk assessment of the change considering the latest product and process knowledge, and not only on the different national and regional requirements. This would also mean that the same PAC could have different categorisation depending on the knowledge and risk assessment outcomes, as illustrated above in Figure 8.4.

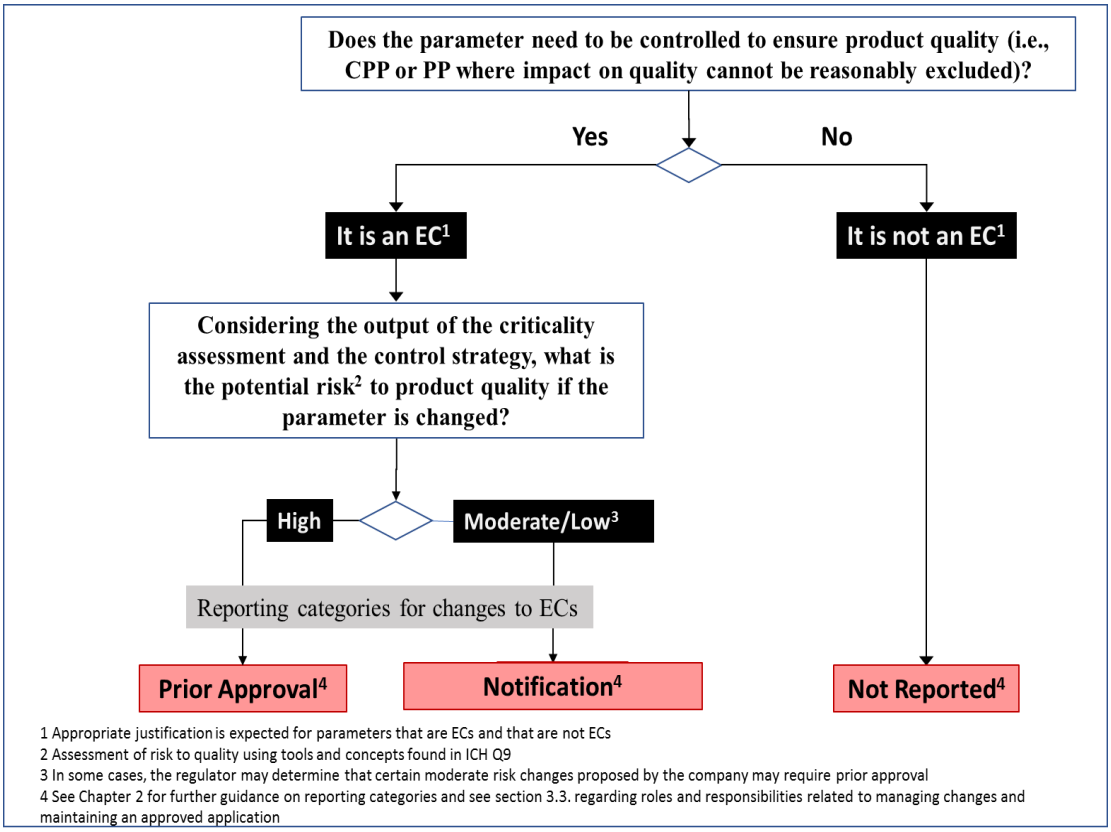

Figure 8.5: ICH Q12 Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters (ICH, 2019)

The ICH Q12 decision tree guides the identification of Established Conditions (EC) and determination of reporting categories. It classifies parameters as ECs or not. Changes to a parameter that is not an EC, does not need to be reported to regulatory authorities. Where a change is made to an EC, a risk assessment for the change would determine the level of risk to product quality associated with the change. Changes to ECs that present a high risk would need to be reported to regulatory authorities for prior-approval, while changes that present moderate or low risk could be handled as a notification.

Starting with this ICH Q12 decision tree, the *1VQ for PAC* focus group sessions led to expanding upon it and integrating it into each of the steps of the change management process. This enhanced risk-based approach for assessment of a PAC and determination of the regulatory reporting category was the second *1VQ for PAC* solution; this was published along with Solution 1 in the *1VQ for PAC* Solutions Paper in May 2020 (Ramnarine *et al.*, 2020).

The risk-based decision-making process underpinning Solution 2 was as follows:

- During a Change Proposal step, a high-level assessment would determine whether there are any potential impacts to the Quality, Safety or Efficacy (QSE) of the product, or if there any legal or regulatory impacts. If this initial assessment determined there was no QSE or legal or regulatory impact of the change, no further risk assessment would be needed, the change could be managed solely within the company's change management system, and not require any regulatory submission. However, if there was a potential QSE or legal or regulatory impact, a more detailed risk assessment would be needed.
- During the Change Evaluation step, a detailed risk assessment would be performed to assess, based on the latest product and process knowledge, any potential direct or indirect risks to the identity, strength, quality, purity or potency of the product. A list of example risk questions was provided in the published paper to aid with this detailed risk assessment. Integrating the ICH Q12 decision tree, high risk changes to an EC would be categorised as prior-approval, and moderate or low risk changes would be categorised as notifications. Changes to non-ECs would require no regulatory reporting.
- During the Change Implementation, Change Review and Change Closure steps, the risk controls identified through the risk assessment would be implemented through a change implementation plan, residual risks would be assessed for acceptance or further mitigation, and change effectiveness would be evaluated prior to and post-change closure.

Development of this solution involving the risk-based assessments, categorisation and management steps for PACs as depicted in Figure 8.6 below, was led by the researcher:

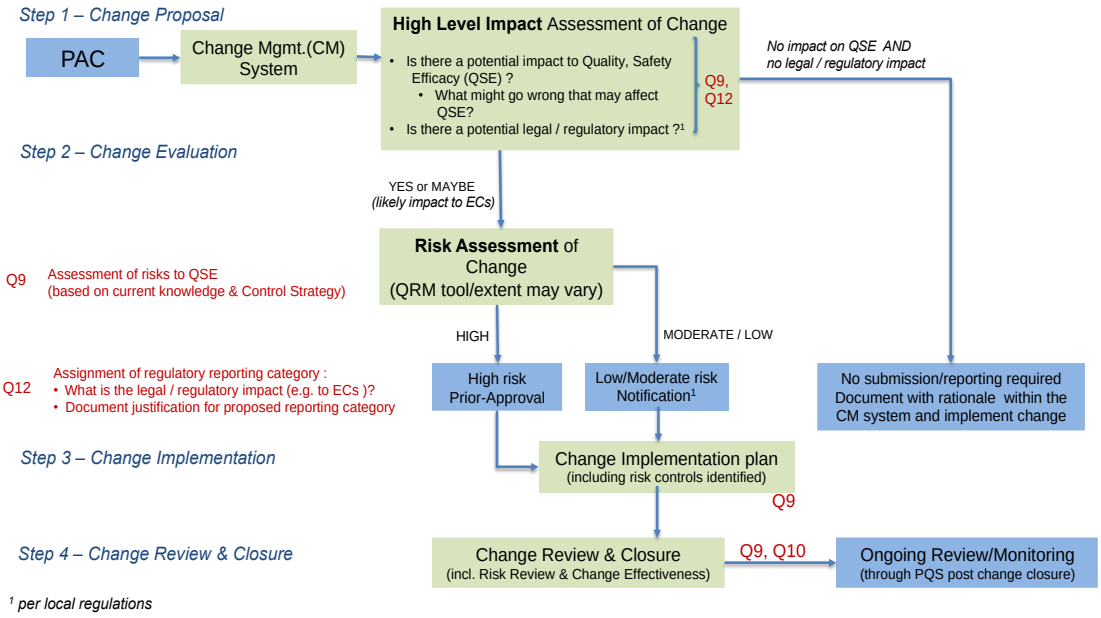

Figure 8.6: Risk-Based Assessment and Determination of Regulatory Reporting Category for a PAC (Ramnarine *et al.*, 2020)

The step-wise details provided in this *1VQ for PAC* solution, if accepted by regulators, would allow companies to know exactly how to apply the concepts of ICH Q9, Q10 and Q12 in a practical and tangible manner, in order to gain the regulatory flexibility and speed of implementation for PACs that, based on product and process knowledge and risk controls, could be managed solely within the PQS or as a notification, without requiring regulatory prior-approval. The company could also use the same risk-based approach for a PAC for all regulatory authorities.

8.4 Solution 3: PIC/S Recommendation Paper - *How to Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management*

As described in Chapter Six, section 6.2 of this thesis, the researcher's discussion with, and her proposal to the PIC/S QRM Expert Circle in 2018, resulted in the development of a practical PIC/S guidance document, for both inspectors and companies, on assessing and demonstrating the effectiveness of a company's PQS in relation to risk-based change management (PIC/S, 2019). The guidance contained a comprehensive checklist that was essentially a tool which gave precise considerations for each of the

key steps of the change management process – change proposal, change assessment, change planning and implementation, change review, and change closure. For each step, it provided a guide on key questions to ask, actions to take, and assessments to make in order to reach relevant decisions. The use of such a clear, practical tool would yield value for both company and inspectors. The benefits of demonstrating the effectiveness of the PQS with regard to risk-based change management would include the timely management of risks to product quality and patient safety, better quality and manufacturing performance, and opportunities for continual improvement and innovation, as envisioned by ICH Q10 Annex 1.

As described in Chapter Six of this thesis, the researcher worked directly with the PIC/S QRM Expert Circle for the development of the paper. The researcher also served as the conduit to the *1VQ for PAC Initiative*, gathering input through the focus groups, and providing to the PIC/S QRM Expert Circle all throughout the paper's development. It was published in November 2019 as a draft Recommendation Paper (PIC/S, 2019) with the intent of having inspectors use it through May 2020, and provide feedback that would be used to finalise the Recommendation Paper.

If a company were to implement the *1VQ for PAC* solutions 1 and 2, as described in sections 8.2 and 8.3, it would be able to provide evidence of an effective science and risk-based change management system as described in the PIC/S Recommendation Paper.

At the 6th focus group session, as described in Chapter Seven of this thesis, the member companies of the *1VQ for PAC Initiative* decided to implement the PIC/S Recommendation Paper. In order to do so, it was necessary to first assess their maturity relative to the PIC/S Recommendation Paper; the next section describes this maturity or gap assessment developed by the researcher and completed by the *1VQ for PAC* member companies.

8.4.1 Maturity or Gap Assessment Completed by *1VQ for PAC* Companies Against the PIC/S Recommendation Paper and Feedback Provided to PIC/S

Prior to implementation of the PIC/S Recommendation Paper, *How to Evaluate and Demonstrate the Effectiveness of a Company's Pharmaceutical Quality System* (PIC/S, 2019), the researcher proposed that the *1VQ for PAC* member companies complete a maturity assessment of their company's change management system against the paper, and also provide relevant feedback to PIC/S prior to finalisation of the paper.

The researcher designed a maturity or gap assessment survey that companies responded to anonymously, communicating the maturity level of their change management system relative to the expectations in the PIC/S Recommendation Paper. The survey questions were developed during the 6th focus group session along with the following maturity scale, which would be used to assess the change management system.

1	2	3	4	5
Undefined Compliance Risk **Don't comply**	Defined – SOP Partially followed **Partially Comply**	Defined – fully followed all the time for changes **Fully comply**	Improved – closed loop feedback **Exceed all expectations**	World Class – **Predictive change management**

To ensure anonymity and confidentiality of the companies completing the survey, the researcher distributed the survey via PDA to the member companies in October 2020 and received the results in November 2020; the results were collated and analysed by the researcher. This also allowed for benchmarking among the *1VQ for PAC* member companies, it provided a macro view of the consolidated change management maturity of those companies, and it helped identify potential improvement opportunities both at a company level and an industry level.

Survey Results (shared with 1VQ for PAC member companies in November 2020)

The survey results were consolidated and shared by the researcher to the *1VQ for PAC* member companies. The survey indicated, overall, that the change management system for most companies fell in the maturity range of 2-3, i.e., partially to fully compliant with the PIC/S Recommendation Paper 's expectations. Only 15-20% of the companies reported exceeding the expectations (maturity level 4), or being at the stage of

predictive change management (maturity level 5); however, even these were only for some, and not all steps. The survey gave participating companies a view into what aspects of their change management systems were mature and where further effort was needed.

The lowest maturity score was related to change risk assessments – 25% of the companies were at a maturity level of 4, and only 1 (out of 22 companies) was at a maturity level of 5 in terms of performing science and knowledge-based risk assessments for changes, and their utilisation for appropriate categorisation of changes. Only 20% of the companies reported a maturity level of 4 in regards to using the outcomes of a change risk assessment to drive change planning, prioritisation, implementation and associated timelines. An opportunity for improvement was also identified with respect to the timeliness of implementing identified risk control measures. Additionally, it was found that evaluation of unintended consequences of risks introduced as a result of the change, or evaluation of residual risk and level of acceptability, was also not mature. The survey results indicated that risk assessments for changes were the weakest link in the change management systems across the companies that responded, and also for the overall pharmaceutical industry. If companies are to gain the benefits of regulatory flexibility for PACs based on science and risk-based application as envisioned by ICH Q8, Q9, Q10, Q11 and Q12, the results of the survey clearly suggested that efforts must be made to improve the use of QRM and KM for proposed changes.

8.4.2 *1VQ for PAC* Comments to PIC/S on the PICS/S Recommendation Paper

The PIC/S Recommendation Paper was published in November 2019 as a draft for a period of a year, to collect feedback on its use prior to finalisation of the document. Therefore, in addition to assessing maturity of their change management systems, the *1VQ for PAC* member companies used the survey results to identify revision suggestions to PIC/S.

No major concerns were identified by the companies that completed the survey, and they classified their comments as high, medium or low in terms of importance, as listed

below in Table 8.1. For sections of the PIC/S Paper not listed in the table below, there were no comments provided.

Table 8.1: Feedback to PIC/S QRM Expert Circle on PIC/S Recommendation Paper

Section of PIC/S Paper	Comments with Rationale	Importance
3.4	Please clarify that the intent is not to verify every single change against this checklist, but to use the Recommendation Paper to assess effectiveness of the Change Management System as a whole by ensuring that the risk-based decision making for changes is appropriate	High
3.5	Recommend adding a statement that the rigor of the risk-based application should be commensurate with the criticality, complexity and impact of the change. This would explicitly clarify that simpler approaches such as a documented risk-based decision rationale can be adequate for simpler changes that should not require use of detailed risk-assessment tools	High
5.1, 1st bullet, and addition of a sub-bullet	• Suggest updating to "….Common lifecycle factors that trigger change include, but are not limited to:" • Suggest updating the 6th sub-bullet under the 1st bullet to "….management review, new or updated regulations….". Though this is not intended to be an exhaustive list, changes in regulations are an important one to call out	Low
5.1, 2nd bullet	Update to "The objectives, scope, description of current state (before the change) and future state (after the implementation), expected outcomes and anticipated benefits of the proposed change are documented. It is important to document current vs. expected future state in the change proposal	High
5.1, 6th bullet	The requirement to document rationale for rejected changes in the statement "For rejected/voided change proposals, the system ensures that the rationales for those rejections are documented, and that continued risks are adequately managed" is an overkill for ALL changes. Propose that a clarification be added to require documentation of rationale for rejections only for compliance/quality/safety/patient impact driven changes. Rejection of a change for edits/corrections is not the same as voiding a change; therefore, suggest addition of the term 'voided" to make this clear.	High
5.2, 1st, 2nd and 3rd paragraphs	• Revise the statement to "However, an impact assessment is often not ~~as~~ comprehensive ~~as a risk assessment for~~ in assessing risks of the proposed change. • Revise the statement to "Therefore, an appropriate	High

	~~structured~~ risk assessment for the change should be performed, and where possible, changes should reduce product quality risks and/or patient safety hazards. • Please add a statement after the above statement "The rigor and approach/ tool selected for the risk assessment may vary depending on the complexity, criticality and impact of the change." • Update the statement to "….knowledge-based risk assessments are performed and documented for changes, taking into account the points below (as relevant to the criticality and risk associated with the change):" • These updates will avoid creating an undue expectation of a detailed structured risk assessment for ALL changes. There is definitely value in doing so for complex changes, but this would be overly burdensome for simple, straightforward changes and will only overcomplicate the change control process.	
5.3, 1st bullet	Update to "The scope, criticality, ~~outcomes of risk assessments~~ and the assigned risk levels drive….". This revision accommodates simple changes that may not have detailed risk assessments	
5.3, 2nd bullet, and 5.4 1st and 3rd bullets	Would be useful to acknowledge by adding a note that change effectiveness can be by means of other parts of the Quality System, such as Quality Systems Management Review (QSMR), Annual Product Review (APR), Continuous Process Verification (CPV), complaint monitoring. If the effectiveness review indicates a negative impact on product quality, actions are assigned as required by the relevant process. This would also help provide a clear distinction between change effectiveness and change acceptance criteria. Acceptance criteria can mean that the deliverables to implement the change were completed as expected; effectiveness looks at long term positive/negative effects and this can be verified through other parts of the PQS	High
5.3, 3rd bullet	Update to "Potential risks with the current state….". Not all changes are a result of compliance/quality/safety/patient issues and may not present any risks to quality, safety or compliance, yet need to be documented in the change control process.	Medium
5.3, 4th bullet	Update to "Interim controls (short-term measures) as needed, are identified and implemented in a timely manner….." This would be an overkill for changes that are not a result of compliance/quality/safety/patient issues.	High
5.4, 1st bullet	Update the statement to "Whenever possible and appropriate, quantitative data are leveraged…." This clarification allows exclusion of simple changes where it is not necessary or value-added to gather quantitative data, even if it is possible	High

Additional comment to support implementation	• Further guidance or implementation materials on how to execute risk assessment for a "critical" change would be helpful. Clear definitions and expectations would aid in understanding the tool. • Further clarity on when a "formal structured risk assessment" should be performed, could also be useful for implementation	High

On behalf of the *1VQ for PAC Initiative*, the researcher sent a letter to Dr Kevin O'Donnell, Chair of the PIC/S QRM Expert Circle on 19-November-2020, providing comments for consideration in finalising the PIC/S Recommendation Paper. All comments were considered by the Expert Circle and most accepted either directly or per intent behind the comment.

The *1VQ for PAC Initiative* reiterated support for the PIC/S Paper as practical guidance that can be used by inspectors and companies alike to assess and/or demonstrate the effectiveness of a company's change management system, and agreed that it would be of fundamental importance in realisation of the ICH Q10 Annex 1 vision.

Furthermore, the researcher proposed a collaboration between the *1VQ for PAC* member companies and the PIC/S QRM Expert Circle in developing further implementation and training materials to jointly advance the respective implementation of the PIC/S Recommendation Paper by the industry and inspectors. Thus far, there has been no formal response from PIC/S on the researcher's collaboration proposal likely because their focus was on finalising and publishing the paper.

8.5 Solution 4: Industry *1VQ for PAC* - Management Review of PACs Guide

Though many companies have Management Review processes and practices in place for their overall PQS, the *1VQ for PAC* focus group sessions highlighted that they did not adequately cover an assessment of how *effective* the PQS was in specifically managing PACs. Current Management Review processes did not have the objective of gaining regulatory flexibility to downgrade PACs from requiring regulatory prior-approval to being managed solely within the PQS.

Towards this end, the researcher, Vinther and Fanzia Mohammed (QMS Head, Roche), developed a draft guide for Management Review of PACs as the fourth *1VQ for PAC* solution. Similar to the other *1VQ for PAC* solutions, this was intended to provide a practical guide to companies identifying important aspects to include in their Management Review activities, in order to evaluate and demonstrate the effectiveness of their PQS for managing PACs. The fundamental premise of this guide was based on the ICH Q10 expectation that:

> *"Senior management should be responsible for pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness."* (ICH, 2008)

This requires senior management to establish an effective PQS including appropriate decision-making processes, and to monitor its effectiveness.

The draft was sent out to the *1VQ for PAC* member companies as a pre-read in advance of the 7th focus group session. Attendees were asked to come prepared with feedback on the content of the document and on the examples provided of Management Review performance indicators.

During the 7th focus group, a session was held on the content of the draft guide, each of the performance indicators and their intent. Comments were received on the draft and specifically on the performance indicators. The guide needed to be as clear and practical as possible, to allow consistent interpretation. Key themes that emerged from the session included:

- refining the intent and clarity of the guide including aligning on terms such as 'new knowledge'
- clarifying why and how Management Review for the overall PQS might not sufficiently assess the effectiveness of the PQS specifically for PAC management, and the ability to gain regulatory flexibility in downgrading changes
- reducing the number of performance indicators to the 1-2 most meaningful ones
- identifying metrics that might already be collected as part of monitoring the overall PQS effectiveness, to minimise or avoid an overlap or redundancy in effort

- understanding the amount of manual effort that might be needed to implement the performance indicators, as if they were too resource or time-intensive, there was a possibility that companies might not implement them
- stressing the importance of the right foundational quality culture, as absent this, the value derived from the guide, or any of the performance indicators, would be limited

Based on the feedback received from the focus group session, the draft guide was updated, and it subsequently went through multiple rounds of reviews and updates, including review by the *1VQ for PAC* member companies, their QMS Heads and CQOs before it was published.

Having discussed the four standard solutions that were developed for science and risk-based assessment of PACs and how to demonstrate effectiveness of the PQS for managing PACs, the next section of this chapter will focus on case studies where the standard solutions 1 and 2 described above were applied to specific PAC examples.

8.6 Application Case Studies: *1VQ for PAC* Example Position Papers

An important aspect of the *1VQ for PAC* solutions is that they describe how the *1VQ for PAC* solutions 1 (*Effective Management of PACs in the PQS*) and 2 (*Risk-based Assessment of Individual PACs*) could be applied to specific individual PAC examples, whereby a company could demonstrate sufficient evidence to support downgrading the PAC from a prior-approval submission to a notification. Towards this objective, the *1VQ for PAC* member companies were asked to provide a list of examples that would benefit from a downgrade. A total of 66 examples were submitted during the second focus group session.

Through the subsequent focus group sessions, participants voted on the list of 66 examples and selected those that would either be quick-wins or would bring broad and large benefits to the industry through their downgrading to notifications for faster implementation. The following 13 PAC examples were selected to develop *1VQ for PAC* industry position papers on:

1. Administrative changes to excipient suppliers (e.g., name change, address change)
2. Drug substance or drug product shelf-life extensions
3. Changes to analytical equipment or instrument that are deemed equivalent to what was already registered
4. Replacement of identification testing of liquid drug substance with visual verification
5. Changes in the size of thermal shipping solution used for transport of product
6. Addition of a testing lab at an existing testing site
7. Changes that bring additional restrictions compared to registered conditions
8. Reference standard changes
9. Drug product batch or scale change with no change to equipment materials of construction or technology
10. Automated colony counter for water, environmental monitoring or product testing
11. Compendial excipient changes
12. Manufacturing equipment or line changes
13. Replacement of Active Pharmaceutical Ingredient (API) suppliers

The intent was to develop each example utilising the published *1VQ for PAC* solutions and to describe the controls that should be implemented within the PQS in a manner that reduced risks to product quality and patient safety, such that the change could be implemented in a timely manner within the PQS, without requiring regulatory prior-approval. These PAC examples also demonstrate application of the ICH Q9, ICH Q10 Annex 1 and ICH Q12 concepts that are expected to enable regulatory flexibility through the application of science and risk-based approaches within the framework of an effective PQS.

The first three PAC examples have been developed by members from the *1VQ for PAC* team (including the researcher), and are published; the next five have undergone peer review, been endorsed by the CQOs and are being prepared for publication, the next two are in development, and work on the last three hasn't been initiated yet. The intent is to continue to add to this list in order to construct a library of PAC examples; this

work will continue with the *1VQ for PAC* member companies even post-completion of this research.

8.6.1 *1VQ for PAC* Position Paper - Managing Excipient Supplier Name and Address Changes in the Pharmaceutical Quality System

The first *1VQ for PAC* example position paper describes how and why simple name and address changes for excipient suppliers can be downgraded from being prior-approval changes to being managed within the PQS only.

Co-authored by the researcher, the first PAC example selected was administrative changes such as to the name or address of an excipient supplier. It was surprising to the researcher that when the *1VQ for PAC* team prioritised the list of 66 examples, this example surfaced as one of the first to develop because one would have assumed that such simple PACs would be easy to make. It became apparent through the focus group discussion that several companies particularly those involved in generics manufacturing, had a high volume of such changes to name and address of excipient suppliers, and they generated high non-value-added workload for their Regulatory Affairs functions. There was unanimous agreement across the member companies that these PACs should not require any regulatory submission in any country. This PAC example was considered a 'quick win', in that if regulators accepted such changes to be ones that could be managed only within the company's PQS, there would be a significant reduction in the effort and lead times that companies encountered through having to file such simple administrative changes for prior-approval in several countries, even though such changes had no impact to product quality and/or patient safety. Most regulatory authorities around the world recognised that these changes could be managed solely within a company's PQS and not require regulatory submissions - but the ones that do require submission for approval generated work for both the companies and regulators that could be easily eliminated without any adverse impact to patients or product. Given that these changes are entirely administrative and, in many cases, retrospective, the *1VQ for PAC* member companies took the position that they would stop submitting such changes for prior-approval in the limited number of countries where this practice remained. The position paper was published in 2020

(Rolke *et al.*, 2020) and describes the rationale for why companies should be able to manage these simple changes to an excipient supplier's name and address within their PQSs only.

8.6.2 *1VQ for PAC* Position Paper: Changes to Analytical Equipment or Instrumentation That Are Deemed Equivalent

The second *1VQ for PAC* example position paper applies the *1VQ for PAC* solutions to an analytical equipment or instrument PAC and describes how a risk-based assessment and specific PQS controls can be used to downgrade the change.

This was the second PAC example selected to develop a position paper on; it was co-authored by the researcher and published in the December 2020 peer-reviewed Journal of Validation Technology (Rolke and Ramnarine, 2020).

The primary premise for this example was that changes deemed 'like for like', or equivalent, could be downgraded from being prior-approval submissions to being managed only within the PQS, because they presented no added risks to product quality and/or patient safety, and the regulatory risk of such changes was minimal. The paper describes the term 'like for like' as one where:

> *"replacement, retirement or decommissioning does not cause any change in analytical methodology, method principles, method parameters and method validation as defined by ICH Q2(R1), analytical specifications, or system suitability, and/or where full method re-validation is not required, and equivalency has been demonstrated."*

In other words, the change is such that it could be managed solely within an effective PQS, without needing additional regulatory approval. The paper further asserted that such changes should not be assessed as regulatory impacting only because the filed dossier included details such as part, model or version numbers, equipment brand names, etc., which when changed typically trigger an update to the filing – there is no regulatory requirement after all to provide such details in the dossier. A revision to the dossier to update or remove such details could be done at a future opportunity when a regulatory impacting revision is needed to the filing.

Experiences shared by the *1VQ for PAC* member companies during the focus group sessions indicated that such changes to analytical equipment or instrumentation were common across all companies, and represented significant non-value-added resource and effort from QC and regulatory functions. The current state resulted in the continued use of outdated or unreliable equipment models, parts or software by QC laboratories, even when the vendor could no longer repair or replace them, and even when better or newer replacements were available. This invariably resulted in deviations, unreliable results or data integrity concerns, in addition to unnecessary investigations, rework or retesting – all of which could be entirely avoided if the equipment, parts or software could be simply replaced with the latest or better versions.

The position paper articulated a sound science and risk-based rationale, and a list of relevant controls that, when documented and demonstrated within the company's PQS, should allow companies to implement these simple 'like for like' (or equivalent) changes to analytical equipment in an expeditious manner without regulatory approval.

8.6.3 *1VQ for PAC* Position Paper: Shelf-Life Extensions for Pharmaceutical Products

The third *1VQ for PAC* position paper describes how shelf-life extension PACs for pharmaceutical products can be downgraded from prior-approval submissions to notifications.

This third *1VQ for PAC* position paper was published in the December 2020 peer-reviewed Journal of Validation Technology (Egal and Lombardi, 2020). The researcher did not co-author it, but was active in its development, and drove all the reviews and endorsement (by *1VQ for PAC* member companies and their QMS Heads and CQOs), and publication steps.

The paper explained that the initial product shelf-life, usually based on limited stability data, is approved as part of the product registration filing. As ongoing stability monitoring provides further supporting data, companies typically extend the approved shelf-life post-authorisation via PAC submissions. In most countries this change is handled as a regulatory prior-approval submission or notification. The paper identified 60 countries where shelf-life extensions must be filed as a major or minor variation,

each requiring regulatory approval. Only the US allowed shelf-life changes to be submitted via a lower notification reporting category, accompanied by an approved stability protocol for shelf-life extensions; India was the only other country allowing for a simple notification of shelf-life changes.

The paper provided 3 case studies on the current state and the proposed future state of faster implementation that could be achieved through application of the *1VQ for PAC* solutions described in sections 8.2 through 8.4. This downgrading of the change is dependent on a company's ability to demonstrate that all underlying risk controls that mitigate potential risks of a product failing its shelf-life specifications were adequate, and that the company had an effective quality system. The paper provided a listing of controls in addition to stability data that would be important in supporting product shelf-life extensions. In the event such controls and supporting data could not be demonstrated, the company would be required to file the change as a prior-approval submission, meaning that the product shelf-life could not be extended until approved by all relevant regulatory authorities – this could take several years. Therefore, it would be to a company's advantage to implement the *1VQ for PAC* solutions and follow this position paper for immediate implementation of shelf-life extensions.

This chapter described all the solutions that resulted from this research study including application position papers for specific PAC examples. The next part of the thesis summarises the outcomes, impacts and conclusions of this research study, and identifies opportunities for future research.

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

Part Six brings the research study to a close with a review of the outputs, outcomes, and impact of this research. Though this research started pre-pandemic, this concluding section of this report articulates key learnings and opportunities that the pandemic has brought forward or underscored. Part Six concludes with recommendations for potential opportunities and focus areas for future research. It includes the following:

- Outputs, outcomes and impacts of this research study (Chapter 9).
- Research conclusions, and pandemic observations, learnings and opportunities for future research (Chapter 10).

Chapter Nine

Outputs, Outcomes and Impacts of Research Study

This chapter describes the outputs, outcomes, and impacts from this research study. It is noteworthy that, as true of all 'wicked problems', while some near-term impacts can be known and other longer-term ones can be anticipated, realising the bottom-line value to patients and public health will be a multi-year, multi-phased, multi-pronged journey. This concept is further elaborated upon in this chapter and also in the next Chapter Ten in the context of post-pandemic and future research considerations.

The University College Dublin's (UCD) Research Impact toolkit illustrated in Figure 9.1 below is being used as a framework to lay out the outputs, outcomes and impacts of this research study (UCD, no date).

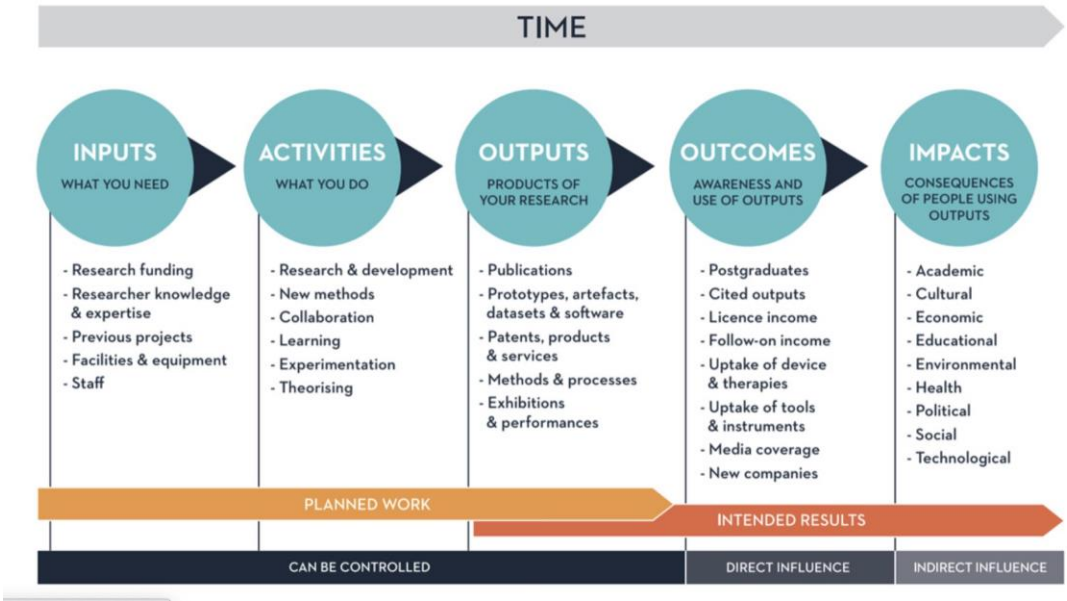

Figure 9.1: UCD's Research Impact Toolkit (UCD, no date)

As described in Chapter Three of this thesis, this research used a mixed methods approach involving focused group sessions with targeted stakeholder groups, KOLs, and decision makers within the pharmaceutical sector. The body of work (both in-development and outputs) from this research was disseminated by the researcher

through a variety of methods and channels, including peer-reviewed publications, presentations, focus group sessions, direct dialogue, surveys, podcasts, social media articles and blogs, and formal or informal interviews with stakeholders and KOLs. These methods and channels are summarised in table format in Table 9.1.

Table 9.1: Methods and Channels the Researcher used for Research Dissemination

Methods of research dissemination (how)	Count	Channels (with whom research was disseminated)
Total Papers	**14**	• Industry *1VQ for PAC* Forums • CQO Forum • QMS Heads Forum • PDA (PAC iAM^{SM} Task Force, conferences, workshops, Advisory Board, Board of Directors) • PIC/S QRM Expert Circle Coordinating Committee • PIC/S Inspectors' Training Events on QRM • Closed Discussion Sessions with Regulators (PIC/S, FDA, WHO) • TU Dublin PRST lectures • IVT Network • Interviews and Discussion Sessions (regulatory authorities, industry leaders, KOLs and SMEs)
Total Papers (as lead author)	10	
Peer-reviewed papers (in journals)	11	
1VQ for PAC Industry Position Papers (published)	6	
1VQ for PAC Industry Position Papers (in peer review)	5	
Proposals to Regulatory Authorities (FDA, PIC/S, WHO)	3	
Surveys	2	
Technical Report	1	
Commentary	2	
Focus Groups	**18**	
Industry *One-Voice-of Quality* Focus Group Sessions	8	
CQOs Focus Group Sessions	6	
QMS Heads Focus Group Sessions	4	
Conference presentations	10+	
Panelist	8+	
Podcasts and Webinars	3	
Social media posts (1500-2000 hits per post)	5+	
Guest Academic Lectures (TU Dublin)	2	
Advisory Board presentations	2	

9.1 Key Research Themes

The resulting outcomes and impacts of the research study can be grouped under several themes. These themes, though distinct, are not mutually exclusive and, therefore, the

related outputs and resulting impacts may deliver value across more than one theme. The four major themes for the outputs, outcomes and impacts of this study are as follows:

1. Global recognition by regulators (for the first time) of the problem of PAC management
2. Influencing the development of regulatory guidances with respect to PAC management
3. Unifying the pharmaceutical industry (for the first time) on the topic of PAC management
4. Practical application of ICH Q9, Q10 Annex 1 and ICH Q12 by development of standard solutions and position papers for selected PACs, incorporating evidence-based QRM

Each of these themes, their specific outputs resulting from this research study and their associated outcomes and impact, as currently known and anticipated, are discussed below.

9.1.1 Key Research Impact Theme 1: Global recognition by regulators of the PAC management problem and its impact

Before any problem can be solved, recognition that a problem exists and can be sufficiently described, is essential. This may not be easy for complex problems, but through the body of work leading up to this research, and even as it proceeded towards defining and scoping the problem, it became evident how much more challenging alignment of a problem definition across the involved stakeholders was for this research, arguably on account of it being a 'wicked problem'. This research served to validate one of the typical characteristics of a 'wicked problem' – that the 'wicked problem' of drug shortages even in its relation to PAC management, continual improvement and innovation, is unique and difficult to clearly define where stakeholders may agree on the nature of the problem and on the importance of addressing it, but they may each view the problem, and therefore its possible solutions, differently, from their own angle.

A key outcome for this research was a graphic representation of the global problem (Figure 9.2) which made it irrefutable for the pharmaceutical industry and regulators alike that:

1. this is indeed a problem,
2. it is a global problem, and
3. its solutions need to be global.

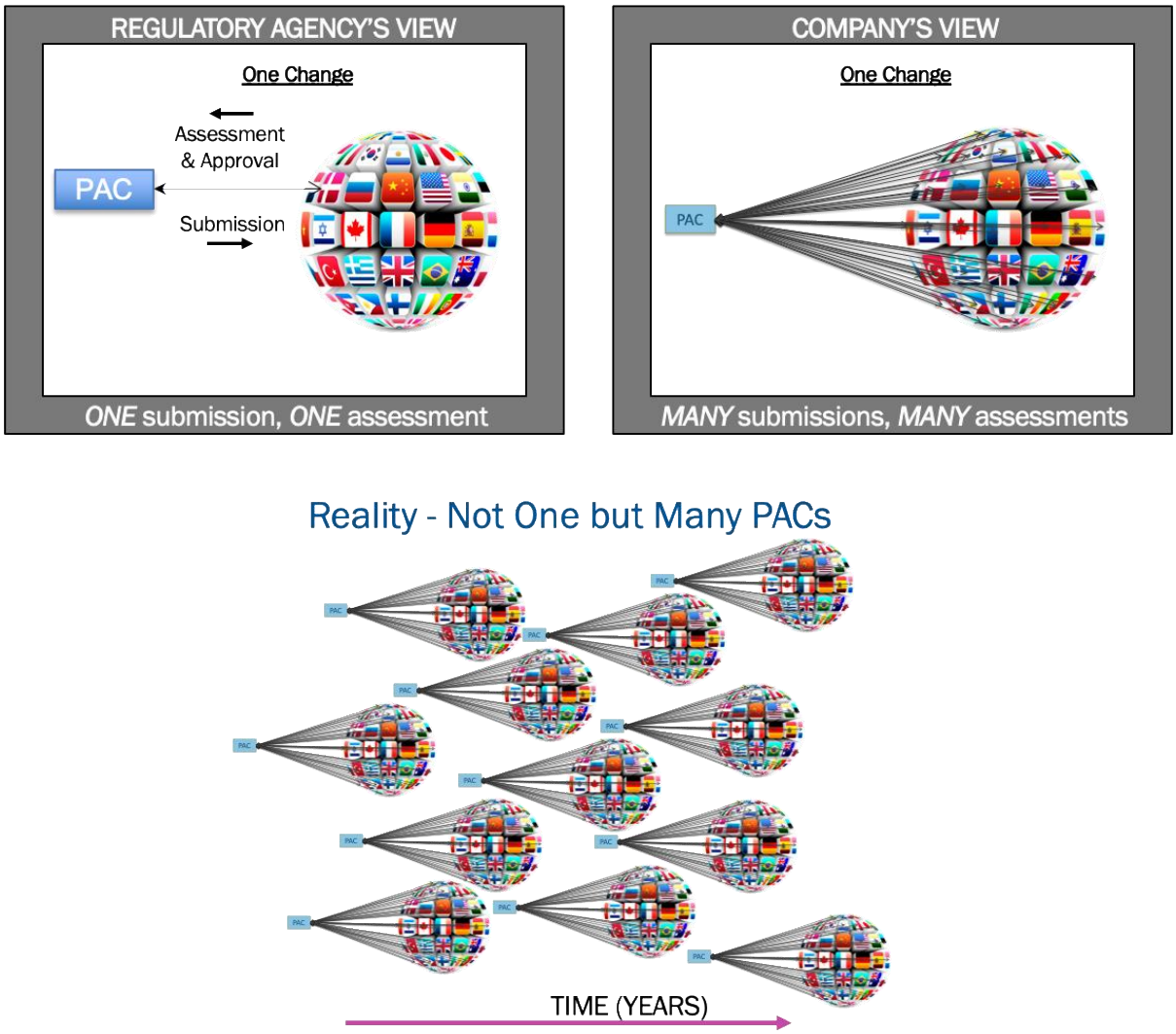

Figure 9.2: Impact of Various Options to Reduce Global PAC Complexity

This graphic became the basis to drive numerous discussions with stakeholders and KOLs across the pharmaceutical sector. It became the basis for the development of the *1VQ for PAC* Concept Paper (Vinther and Ramnarine, 2019b), which aligned the senior-most Quality leaders from 30 global pharma companies and gained their commitment to develop and implement standard solutions across the industry. It is also

noteworthy that this graphic helped elevate the recognition of the problem across ICH and non-ICH countries. It has been cited in presentations, including a confidential reflection paper used to align regulators which was shared with the researcher, the ICH Management Committee, ICMRA and PIC/S.

9.1.2 Key Research Impact Theme 2: Influencing regulatory activities and development of regulatory guidance related to PAC management

This was the first time the problem of global regulatory complexity and its impact on slow PAC management, was elevated to the level of a global unifying call to action for standard solutions, both within the worldwide industry and regulator communities, with the following occurring:

1. PIC/S and the global inspector community recognising and activating to develop a solution to assess and demonstrate an effective PQS to support PAC management and other areas
2. ICMRA activating a coordinated pharmaceutical knowledge management strategy to enhance regulatory reliance and agility (ICMRA, 2021)
3. the WHO accepting the researcher's [6] proposal to collaborate with pharmaceutical companies and work further towards reliance through pilots on specific PACs applying the *1VQ for PAC* solutions

The contribution of this research study to the recently finalised and published PIC/S Recommendation Paper (PIC/S, 2021) and the researcher's leadership all through its development, pilot and finalisation were acknowledged by the PIC/S Chair, Dr Anne Hayes, when the paper came into force on July 15, 2021 by a personal email to the researcher which stated:

> *"I know that you've contributed significantly to the development of this PIC/S Recommendation and I just wanted to say 'thank you' for your great work on this."*

[6] Co-developed with Vinther

The PIC/S QRM Expert Circle Chair, Dr Kevin O'Donnell also recognised the researcher's contributions in a letter sent to the researcher on 13-July-2021, specifically stating:

> *"Your presentation at the PIC/S Quality Risk Management (QRM) Expert Circle meeting in Taiwan in September 2018, in relation to risk-based change management, continual improvement, post-approval change management and drug shortages, was absolutely fundamental in driving the development of the paper, as from that presentation and discussion came the agreement and the impetus to develop the paper. The paper, however, would not have come to fruition without your continued involvement in it following that meeting in Taiwan."*

The published *1VQ for PAC* standard solutions paper (Ramnarine *et al.*, 2020), endorsed by CQOs from 25+ pharma companies, was another output that has led to regulators such as WHO, PIC/S and FDA being willing to enter into direction-setting discussions and possible case study application pilots with the senior-most industry Quality leaders. This has the potential to drive unprecedented collaborations in this area of work between the pharmaceutical industry and regulatory authorities at a global scale to drive better science and risk-based decision making both by companies and regulators based on latest product and process knowledge. It also has the potential to further facilitate regulatory reliance opportunities using actual case studies from companies that can enable risk-based decision-making alignment between countries. It is anticipated that the science and reliance basis will be highly impactful levers, as elaborated further in Chapter Ten, section 10.3 of this thesis, to accelerate implementation of PACs, thereby speeding up continual improvement and innovation in the pharmaceutical industry for the ultimate impact to patients – the on-time and reliable availability of medicines for patients anywhere in the world.

9.1.3 Key Research Impact Theme 3: Unifying the Pharmaceutical Industry on PAC Management

The *1VQ for PAC* focus group sessions co-led by the researcher with pharmaceutical companies and their Senior Quality Leaders (CQOs and QMS Heads) led to unifying 30 global companies for the first time, resulting in:

- The creation of a new stakeholder community of Senior Quality Leaders – this group is setting the strategic direction for the pharmaceutical industry on reducing regulatory complexity through improved science, QRM and an

effective PQS. They are owners of their company's PQS and are accountable for all product quality and cGMP compliance decisions. Therefore, this stakeholder community has the potential to set the direction on broader and other impactful Quality topics. They can be key in shifting the operational direction of the industry from rule-based to risk-based to evidence-based and risk-informed decision-making.

- Unified industry standard solutions and commitment from their senior-most Quality leaders to implement practical solutions for PAC management. This will enable building more trust of the industry by regulators, leveraging the strength of an effective and mature PQS and the role of Quality in timely and fast decision-making, such that greater regulatory flexibility becomes possible. These standard solutions align with other sectors such as the medical device industry, which relies on standards, such as ISO to inform and drive decision making, while continuing to innovate and improve.
- Transformation of PAC management through improved science and risk-based decision making and an effective PQS, such that more changes can be managed only within the PQS and fewer PACs need to be submitted to regulatory authorities for approvals. This would be highly impactful in accelerating continual improvement and innovation in the pharmaceutical industry, via the faster implementation of changes, while significantly reducing the resource, effort and lead time burden on both industry and regulators. The regulatory oversight for the changes shifts from the assessors reviewing and providing prior-approval for certain PACs to the inspectors during inspections verifying the effectiveness of the PQS in adequately managing PACs, facilitates a more timely implementation of changes which allows the industry to continuously improve and innovate faster.

9.1.4 Key Research Impact Theme 4: Practical application of ICH Q9, Q10, Annex 1, and ICH Q12 case studies for PACs

The body of work from the *1VQ of PAC* focus groups led, for the first time, to practical application information including specific PAC example position papers on 'how to'

implement the high-level concepts and requirements from ICH and other regulatory guidances. This, along with the commitment from CQOs to implement these concepts within their companies, will facilitate implementation of the standard solutions, increased acceptance by regulators given consistent application, collective learnings, collaboration with regulators, and evolution based on shared experiences and learnings.

These PAC example position papers provide practical application case studies of Lipa's Risk Knowledge Infinity (RKI) Cycle for product lifecycle management, as published in 2020 and 2021, and shown in Figure 9.3 below (Lipa, O'Donnell and Greene, 2020; Lipa *et al.*, 2021).

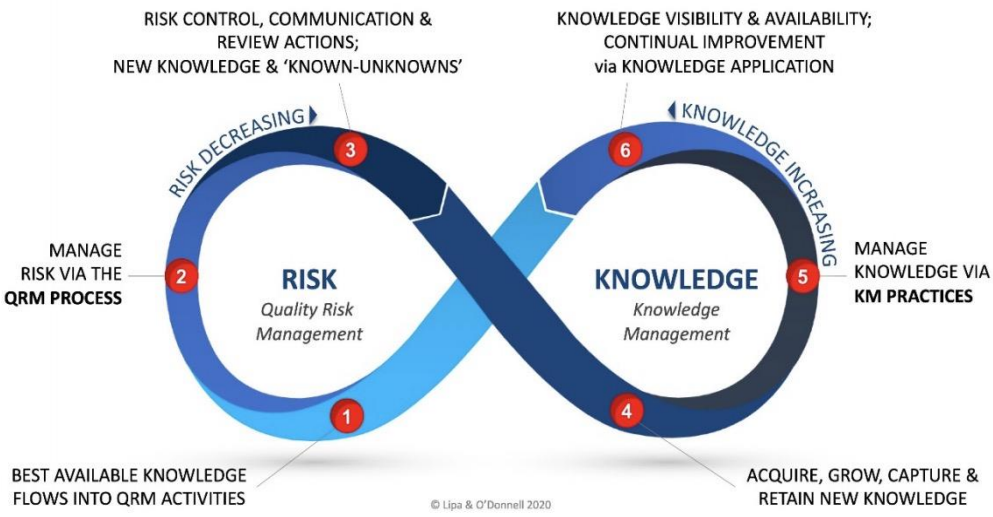

Figure 9.3: The RKI Cycle as Applied to ICH Q10 (Lipa, O'Donnell and Greene, 2020)

Gaining regulatory flexibility can be co-related to increased product and process knowledge, leading to better risk controls and thereby lowering product quality and/or patient safety risks. The published PAC example position papers described in Chapter Eight, section 8.6 of this thesis, are also case studies that demonstrate application of the RKI cycle (as described by Lipa and illustrated via various case studies (Lipa *et al.*, 2021)); this is because increasing knowledge and decreasing risk should make these PAC examples viable candidates for:

- Downgrading to a lower change category, thereby allowing greater regulatory flexibility as envisioned by ICH Q10 Annex 1

- Gaining trust from regulators on managing more PACs within an effective PQS, (demonstrated via the *1VQ for PAC* solutions (Ramnarine *et al.*, 2020) and the PIC/S Recommendation Paper (PIC/S, 2021))
- Shifting from rule-based or compliance-based decision-making to risk-based decision-making, and further improving towards evidence-based and risk-informed decision-making
- Faster implementation of PACs, thereby accelerating continual improvement and innovation
- Ultimately leading to the on-time and reliable availability of medicines for patients anywhere and everywhere in the world

All of these outputs, outcomes and impacts signify the value that can be delivered near-term and longer-term towards the 21st century vision of:

> "*a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.*" (FDA, 2004)

9.2 Summary of Research Study Outputs, Outcomes and Impacts

Table 9.2 provides a summary of the four key research impact themes mapped out for outputs, outcomes and impacts per Figure 9.1. It should be noted that several outputs and impacts are not exclusive to only one research impact theme, as they are expected to deliver value across multiple themes.

Table 9.2: Mapping Key Research Themes to Outputs, Outcomes, and Impacts

Key Research Impact Themes	**Outputs** | Products of research	**Outcomes** | Awareness and use of outputs	**Impacts** | Consequences of people using outputs (planned or anticipated)
1. Global recognition by regulators (for the first time) of the problem of PAC management	• Industry Concept Paper: *1VQ on PAC*s (requested by FDA CDER Head and Acting Commissioner Dr Janet Woodcock and FDA senior staff) • A graphical depiction of the global problem (Figures 1.1 and 1.2 cited in papers and presentations by regulators and KOLs) • Survey: Impact of global complexity for PACs • Various publications and presentations on problem and solutions • Social media posts and podcasts addressing problem and disseminating solutions for PAC management	• ICMRA and ICH Management Committee Reflection Papers cited research content and graphics – signals unprecedented recognition by regulators of the global PAC problem and its impacts • Increased dialogue on regulatory reliance. ICMRA Reflection Paper and ICMRA's coordinated pharmaceutical quality knowledge management strategy to enhance regulatory reliance and agility is evidence of authorities coming together to evaluate possible solutions • EC's 2021 'Structured Dialogue on Security of Medicines Supply Initiative' recognised need for standardising regulatory procedures for PAC management across EU and globally • WHO' interest in collaboration and pilot with the CQOs • Shift from a problem to a solutions mindset – based on science and risk • Acknowledgement that public health is a *global* matter, and PAC management cannot be addressed at	• A unified pharmaceutical industry (~30 top global pharma companies coming together) for the first time to propose solutions for better science and risk-based decisions • A public health issue being addressed as a global matter • Faster global approval of PACs (from years to months) • Regulatory authorities collaborating to design and implement solutions to facilitate faster PAC approvals • Better use of regulatory authority resources – due to fewer PACs needing approvals (can allow focus shift to other important issues) • Impact of future research to be determined with continued focus on 1) faster approval timelines for more PACs by more regulatory agencies and 2) fewer PACs requiring pre-approvals

Key Research Impact Themes	**Outputs** | Products of research	**Outcomes** | Awareness and use of outputs	**Impacts** | Consequences of people using outputs (planned or anticipated)
		fragmented local or regional levels	
2. Influencing regulatory activities and development of regulatory guidances related to PAC management	• Presentation and proposal to PIC/S QRM Expert Circle on PQS Effectiveness and risk-based PAC management • *1VQ for PAC* Solutions paper – how to perform risk-based PAC assessment and demonstrate effective PQS for PACs • Practical PAC management example case studies published – case studies that companies can implement as is • Proposal to WHO for collaboration and pilot • High level concepts and text content for ICH Q12 (specifically Product Lifecycle Management Plan, Change Management and PQS sections) • Submission of consolidated industry *1VQ for PAC Initiative* feedback to FDA on ICH Q12 guidance and European Commission's Strategy for Timely Patient Access to Affordable	• Clear approach on 'how to' apply practical, science and risk-based PAC management with case study examples • PIC/S guidance developed (in collaboration with researcher) and published on 'how to demonstrate effectiveness of the change management system' • Active input, endorsement and adoption of the PIC/S guidance on risk-based change management by the top 25+ global pharma companies • Industry's assessment of its maturity, gaps and remediation against the *1VQ for PAC* PQS solution paper and the PIC/S guidance • ICMRA Reflection Paper and ICMRA's published coordinated pharmaceutical quality knowledge management strategy to enhance regulatory reliance and agility	• Implementation of the practical *1VQ for PAC* solutions and PIC/S guidance will facilitate regulatory flexibility for PACs, per ICH Q10 Annex 1 • Better science and risk-based change management decisions and processes • Improved PQS maturity for faster PAC implementation • Implementation of ICH Q10 Annex 1 by regulatory authorities • Consistency during inspections in evaluation of companies' change management processes (PIC/S, 2021) • Potential to drive more collaboration (regulatory authority ←→ regulatory authority and regulatory authority ←→ industry) • Potential to increase mutual reliance between regulatory agencies • **On-time and reliable availability of medicines for patients anywhere and**

Key Research Impact Themes	**Outputs** | Products of research	**Outcomes** | Awareness and use of outputs	**Impacts** | Consequences of people using outputs (planned or anticipated)
	Medicines		**everywhere in the world**
3. Unifying the pharmaceutical industry (for the first time) on PAC management	• Published *1VQ for PAC* Industry Concept Paper • Published *1VQ for PAC* standard global solutions: 1. Risk-based decision tree for PACs 2. How to demonstrate an effective PQS for PACs • Various publications and presentations (summarised in Figure 1.10)	• Endorsement and commitment by the CQOs of 30 global pharma companies (first time senior-most Quality leaders speaking with one voice and willing to have their names and company names listed on published papers) to solve this global PAC problem with standardised and practical global solutions • Created a new stakeholder community of Senior Quality Leaders that are now mapping a more strategic direction for the industry on not just the 'what' but also the 'how' in relation to science and risk-based Quality decision making and PQS topics • Unified communication, messaging and exchange between industry Quality leaders and regulators • Standardised and practical solutions that, for the first time, address how PACs can achieve faster approvals in both ICH and non-ICH countries • Facilitate regulatory flexibility per	• Mechanisms whereby companies can routinely request regulatory flexibility based on product and process knowledge, risk-basis and an effective PQS • Faster global approval of PACs (from years to months) with more consistent risk-based decisions across countries • More PACs managed only in the PQS; greater trust in industry, leveraging the role of Quality (e.g. QP and QA) for quality decisions) • Increased science basis and more regulatory reliance and collaboration • Accelerate innovation and continual improvement in the pharma industry • Less burden (resources, effort and time) on companies and regulatory authorities for PACs • The CQOs stakeholder group can be key in shifting the industry from rule-based to

Key Research Impact Themes	**Outputs** | Products of research	**Outcomes** | Awareness and use of outputs	**Impacts** | Consequences of people using outputs (planned or anticipated)
		ICH Q9 and Q10 Annex 1, when risk and evidence-basis is presented by companies	risk-based to evidence-based and risk-informed decisions • **On-time and reliable availability of medicines for patients anywhere and everywhere in the world**

4. Practical application of ICH Q9, Q10 Annex 1 and ICH Q12 case studies for PACs	• ICH and other regulatory guidances have provided the 'what' concept and requirements that companies must follow. This is the first time detailed practical application information was made available on 'how to' implement those concepts at an operational level
	• Published *1VQ for PAC* solutions paper - this directly supports ICH Q10
	• Published specific PAC example case studies illustrating application of the solutions
	• *1VQ for PAC* website
	• Various publications and presentations (summarised in Figure 10.1)
		• Rediscovery and increased focus on ICH Q10 Annex 1 – raising accountability of both industry and regulatory authorities to implement
		• *1VQ for PAC* becoming a unified voice on PQS and Quality at a broader level for greater impact – as evidenced by published industry position papers and case studies
		• Recognition by regulators and industry that the latest product and process knowledge is not being implemented as fast as necessary
		• PAC case studies demonstrating
		  ○ evidence-based QRM and the Risk Knowledge Infinity (RKI) cycle for product lifecycle management
		  ○ step-wise approach companies can use to accelerate implementation of new product and process knowledge
			• Increased number of science and risk-based decisions by both companies and regulators for PACs
			• Consistent and standardised global practices across industry and regulatory authorities for specific types of PACs
			• Implementation of ICH Q10 Annex 1 by regulatory authorities with regard to regulatory flexibility for PACs based on demonstrated PQS effectiveness
			• Additional guidance and collaboration from regulatory authorities (via ICMRA) in relation to PAC management
			• **On-time and reliable availability of medicines for patients anywhere and everywhere in the world**

This chapter summarised the outcomes and impact of this research study designed and conducted in a pre-pandemic context. The next chapter draws on some of the insights and learning acquired from the COVID-19 pandemic, and expands on future research opportunities that could extend from this research study and its conclusions.

Chapter Ten

Research Conclusions and Opportunities for Future Research

This chapter draws conclusions on the research study. As stated in Chapter One, section 1.3 of this thesis, the overarching goal of this research study was **to accelerate continual improvement and innovation, and reduce global complexity through science and risk-based transformation of PAC management– so that the pharmaceutical sector can ensure the uninterrupted delivery of safe, effective high-quality medicines to patients.**

This research was conducted at an opportune time, when there was a heightened focus, momentum and interaction across key stakeholders - regulatory authorities, pharmaceutical industry, policy makers, patients, governments - towards the objectives of reducing global drug shortages, improving product lifecycle management, and advancing innovation to address unmet medical needs. This research study resulted in practical science and risk-based solutions that, if implemented by pharmaceutical companies and regulators, could meaningfully contribute towards addressing the 'wicked problem' of drug shortages, by facilitating faster continual improvement and innovation for medicinal products throughout their commercial life. This would be based on implementation of new knowledge gained closer to real-time, instead of taking years.

The final stages of this research occurred during the course of the global COVID-19 pandemic. This was entirely unanticipated in the initial research plan, and while the research plan evolved during the course of this study, it was decided not to extend the research to delve deeply into pandemic-related changes and post-pandemic learnings. This was primarily because the pandemic is still ongoing and the regulatory authorities, pharmaceutical industry, healthcare sector and policies are continuing to evolve. Nevertheless, in this concluding chapter, in addition to the research conclusions and considerations for future research, the researcher has highlighted aspects of the COVID-19 pandemic that are pertinent to this research and which are anticipated to alter the

future state of PAC management, product lifecycle management, and ultimately, the pace of continual improvement and innovation at a global level in the pharmaceutical sector. These are therefore, also expected to inform and influence future research into these topics.

10.1 Some COVID-19 Pandemic Observations: Increased Focus on Public Health

The COVID-19 pandemic started in the small Wuhan region in China towards the end of 2019, but ballooned to a global scale at an unprecedented pace in a matter of weeks; it has had a global public health impact of a magnitude that no single country had anticipated or was even remotely prepared for. As each country worked hard and fast to contain, control and manage the pandemic at a national level, it quickly became apparent that all countries were facing similar daunting challenges, and many of the mitigating actions taken at a national level could have been (but were not), proactively and quickly leveraged across countries. Each country struggled to adapt their practices, processes, and policies, and to implement pandemic control measures based on their individual experiences and learnings. Though similar lessons were being learned across countries, with some being fairly basic and obvious, such as the importance of masks, social distancing and hygienic practices, it was interesting and intriguing to note that each country became more inward-focused. The lessons learned in one country did not necessarily and adequately translate to lessons adopted in others, as quickly as they could and should have. Similar to the topic of this research, where solving a global problem at a global level should be intuitive and primary, all action has tended to be at smaller, national (not even regional) levels with a ‘country-first’ mindset. One wonders whether this might be because these problems and their solutions are simply too huge, too ‘wicked’, to tackle at a global scale.

The pandemic has underscored the fact that diseases know no borders, patient and public health needs largely do not vary by country, and therefore, solutions must be global in nature. The pandemic forced the pharmaceutical industry, regulatory authorities, supply chains, distribution networks, governments, policy makers, societies and communities as a whole to flex and adapt in a manner and at a scope that had not been envisaged or planned for. Though pharmaceutical companies and regulators have

always had the primary objective of serving patients, with the COVID-19 pandemic, the need to be unequivocally patient-centric, emerged as the singular unambiguous objective.

The worldwide outbreak of COVID-19 highlighted that the current regulatory frameworks both at national and global levels were not designed for, or capable of, managing through a pandemic. Managing drug shortages had already been a global challenge pre-pandemic; the pandemic further exacerbated this challenge, threatened the availability of critical medicines including those needed for COVID-19 patients, and it impacted people's lives in a manner and scale that the world had never experienced before.

Pharmaceutical companies and regulatory agencies across the world realised that standard ways of working were not effective, or even possible, in several regards due to pandemic-imposed restrictions. Business continuity mode in significant facets of the pharmaceutical, regulatory and healthcare sectors had to be activated, and greater flexibility in making, assessing, and releasing products, and administering patient care, became essential. Greater flexibility was afforded by regulatory agencies to manufacturers and marketing authorisation holders without compromising the safety, quality and efficacy standards for medicines in order to mitigate drug shortages. Public health was elevated to a more prominent, front-and centre-stage as the world raced to overcome the catastrophic impact of a virus that had shutdown countries and economies globally within weeks. Even so, providing medicines to patients was not something that could be deferred, delayed or shut down – the public health crisis caused by the pandemic had to be dealt with swiftly.

10.1.1 Regulatory Flexibility to Mitigate COVID-19 Related Public Health Consequences

Ensuring the availability of critical medicines became a public health priority during the pandemic. Within a month after the COVID-19 outbreak was declared a global pandemic on March 11, 2020 by the WHO (Cucinotta and Vanelli, 2020), the EMA, together with the Heads of Medicines Agencies (HMA) and the European Commission (EC), published an important Questions and Answers paper on 10-April-2020, on

Regulatory Expectations for Medicinal Products for Human Use During the COVID-19 Pandemic (EMA, HMA and EC, 2020). This notice to stakeholders granted immediate regulatory flexibility to mitigate drug shortage and supply continuity risks due to supply chain or manufacturing disruptions that were a consequence of the extenuating COVID-19 constraints. The Q&A document was revised on 17-April-2020 and 26-May-2020, in order to introduce additional flexibilities.

Some areas of regulatory flexibility granted to manage through the COVID-19 challenges and restrictions on a temporary basis included:

- Companies being able to utilise new manufacturing sites and quality control labs, or alternative suppliers for starting materials, reagents, intermediates, active substances, or finished product, even when these were not specified in the marketing authorisation. This could be done under an Exceptional Change Management Process (ECMP) where such changes were necessary to mitigate drug shortages and supply disruption.
- Potential to postpone renewal of marketing authorisation license when warranted due to COVID-19 constraints.
- Extension of GMP certificates and authorisations to manufacture or import products through the end of 2021 without on-site inspections and on the basis of a distant assessment.
- Acceptance of remote batch certifications and remote audits of active ingredient manufactured by a Qualified Person (QP).
- Flexibility in labelling and packaging requirements to facilitate movement of medicinal products within the EU.
- Flexibility in allowing limited prospective qualification for new manufacturing equipment and facilities, or concurrent validation of manufacturing processes for COVID-19 crucial medicines. This required the application of formal QRM to determine scope of desired flexibility, assure product quality, and it required documentation of all relevant decisions within the PQS and approved by authorised personnel, including the Quality Unit and QP.

In May 2020, to further expand on the Questions and Answers paper, the Co-ordination EU's Group for Mutual Recognition and Decentralised Procedures - Human (CMD*h*)

provided practical guidance on handling and expediting certain regulatory processes during the COVID-19 crisis (CMDh, 2020). The EMA also published initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines (EMA, 2020).

In the US, the FDA, under section 564 of the Federal Food, Drug, and Cosmetic Act, activated its 2017 guidance for Emergency Use Authorization (EUA) of Medical Products and Related Authorities (FDA, 2017). An EUA is a mechanism to facilitate the availability and use of medical countermeasures, including vaccines, during public health emergencies, such as the COVID-19 pandemic. Under an EUA, FDA can authorise use of unapproved medical products or unapproved uses of approved medical products during public health emergencies, to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological, and nuclear threat agents, including infectious diseases when certain statutory criteria are met, or when there are no adequate, approved, and available alternatives. To manage the COVID-19 public health emergency, FDA granted EUAs for several treatments, diagnostic tests and vaccines for the duration of the pandemic.

The flexibility and accelerated timelines for marketing authorisations, post-authorisation or emergency use authorisation applications were targeted to resolve shortages or availability issues for critical products that were directly intended for COVID-19 use, or for expediting the development and evaluation of treatments and vaccines for COVID-19. The primary focus of all these regulatory efforts was to efficiently manage a public health crisis. They were exactly in the direction of swift and much-needed science and risk-based decision-making, also aligning with the insights and outcomes that emerged from this research study.

Since the regulatory flexibility and accelerated timelines offered by the ECMP during the pandemic were most relevant for this research, in the context of PAC management, the researcher contends that this approach and its intended application could continue to yield valuable benefits even post-pandemic. The ECMP allowed MAHs to implement changes very quickly, by notifying the relevant competent authority within 48 hours of making the change, and without waiting for prior-approval by the regulatory authority. It also required the EU competent authorities to respond back to the MAH within 2

working days and, if they did not raise any objections within the 2 working days, the ECMP application would be considered as accepted (CMDh, 2020; EMA, HMA and EC, 2020).

However, it was made clear that this regulatory flexibility via the ECMP was narrowly restricted:

1. It could ONLY be applied to medicines that were considered crucial for the treatment of COVID-19 patients, and
2. It could ONLY be used to implement changes to manufacturing sites, QC laboratories or suppliers for starting materials, reagents, intermediates, active substances, or finished products that were specifically for COVID-19 treatments.

All other non-COVID-19 related crucial medicines and all other types of post-approval changes (e.g., changes to specifications) were excluded from the ECMP flexibility.

10.1.2 Unprecedented Speed of Innovation and Collaboration from Pharmaceutical Companies

In parallel to the prompt actions from regulatory authorities, COVID-19 propelled the pharmaceutical industry into a broad range of undertakings as well, and at extraordinary speed - from testing and investigating existing medicines as potential treatment options against COVID-19, through rapid clinical trials, and highly accelerated development of novel treatments and preventive vaccines. The standards of care for treatment of COVID-19 hospitalised patients in many countries involved Gilead's antiviral product, Veklury (remdesivir) and the corticosteroid dexamethasone. The FDA granted EUAs for several treatments - convalescent plasma to treat hospitalised COVID-19 patients, Eli Lilly's monoclonal antibodies (bamlanivimab, bamlanivimab+etesevimab), and Regeneron's antibody cocktail (casirivimab and imdevimab), to treat mild to moderate COVID-19, and Eli Lilly's Olumiant (baricitinib) in combination with remdesivir for the treatment of hospitalised COVID-19 patients requiring supplemental oxygen. Per GlobalData, an intelligence gathering resource for the pharmaceutical sector, as of March 2021, a record-breaking 1600+ novel or repurposed drugs were in the global pipeline for COVID-19 treatment, and while 62% of them were in the discovery or pre-clinical stages, 4500+ clinical trials had been initiated and were in progress globally.

The authorised or approved COVID-19 vaccines included Pfizer and BioNTech's Comirnaty (BNT162b2), Moderna's mRNA-1273, AstraZeneca's AZD1222, and Johnson & Johnson's single-dose adenoviral vector vaccine (JNJ-78436735). Additionally, the Russian vaccine, Sputnik V, was made available in several countries, and vaccines from Chinese manufacturers, Sinovac, Sinopharm, and CanSino were authorised in China and several other countries. Vaccine efficacies upwards of 90%, as seen with the mRNA vaccines, were not typical. Yet, as vaccines and treatments were brought to market with extraordinary effort and unmatched speed, the virus, not unexpectedly, has continued to mutate fast, and at accelerating level. New viral variants continued to emerge even as countries urgently worked towards increasing vaccination rates. Several companies, including Moderna and Pfizer, initiated a new wave of development for vaccines and vaccine boosters against the newly emerging SARS-CoV-2 viral variants, soon after their vaccines against the original viral strain had been commercialised.

Vaccines are highly complex biologics to develop, manufacture and supply. Typical development, manufacturing and approval has historically taken 3-5 years and often longer. Having multiple vaccines developed, tested through global clinical trials, and approved in multiple countries in less than a year, with two of them based on a new mRNA technology not approved before, was ground-breaking and pioneering! It is a clear demonstration that this speed of innovation and change is not only needed, it is indeed possible.

The challenges with manufacturing enough doses and making them available globally to treat and vaccinate patients also spurred an exceptional wave of unusual strategic partnerships, agreements and collaborations between pharmaceutical companies – some examples being Roche collaborating with Regeneron to manufacture their antibody cocktail, Novartis producing Pfizer/BioNTech's vaccine to boost global supply, and also manufacturing the mRNA bulk drug for CureVac's COVID-19 vaccine candidate, Merck producing Johnson & Johnson's COVID-19 vaccine, and Sanofi and GlaxoSmithKline partnering to develop a vaccine. Competition became secondary to collaboration in the service of public health, as pharmaceutical companies and regulators spared no effort or resources in the race to deal with the COVID-19 pandemic. Such collaborations were previously more an exception and driven by mutual

benefits to the collaborating companies; but with the pandemic they became the norm, driven by a common, unifying purpose of supplying vaccines and treatments to patients in order to alleviate a public health crisis.

10.2 Learnings from the COVID-19 Crisis

The COVID-19 crisis forced new ways in the application of science and risk-based decision-making by both regulatory authorities and pharmaceutical companies. In this regard, it led to an increased utilisation of the PQS to manage and document changes and decisions, and an increased reliance on the Quality Unit (including the QP) and on QRM to ensure that the granted flexibility and the expedited change processes did not compromise product quality and/or patient safety in any unacceptable way. Without this paradigm shift in operations across the global pharmaceutical sector, public health would have been significantly and unavoidably impacted well beyond that directly resulting from COVID-19 infections, in that patient access to life-saving crucial medicines would have been compromised even more severely.

These provisions may seem new, but their underlying reliance on the PQS, the Quality Unit and QRM and KM to support them reflects what has long been in existence to provide a balanced framework and structure for science and risk-based decision-making, while ensuring that product quality, safety and efficacy remained uncompromised. This was how the ICH Q9, Q10, and Q12 guidances had envisioned their objectives and concepts to be realised. However as acknowledged by both industry and regulatory authorities, practical guidance is needed to implement the concepts and principles in the ICH guidances. This is where unified practical solutions such as those resulting from this research are necessary.

Speed and flexibility are paramount in accomplishing the primary objective of making safe, effective, high-quality products available for patients during the pandemic. During the pandemic, regulators were able to mobilise, debate, align and make important decisions within a matter of weeks on the optimal and appropriate course of actions to prevent a potential public health crisis resulting from drug shortages. Companies were able to innovate and bring products to market faster than ever before. To quote Malcolm

Gladwell, a global thought leader and author on innovation, history, management and leadership:

> *"A sense of urgency and social risk-taking, beyond operational risk-taking is essential."*

The urgency of the COVID-19 crisis enabled a different risk-benefit view. The swift actions taken by regulators and companies to overcome manufacturing and supply disruptions, were exemplary and laudable (clearly demonstrating that it could be done when needed), but it also raised some obvious, thought-provoking questions and lessons from the pandemic that the pharmaceutical and regulatory sectors should consider going forward:

- Why did it take a significant crisis like COVID-19 to realise the regulatory flexibility and speed that had already been envisioned for over a decade via ICH Q10 and Q9?
- Why was the applicability of the flexibilities introduced in 2020, which relied heavily on science and risk-based decision-making, strictly limited to medicines considered crucial for COVID-19 treatment?
- Why were these provisions for regulatory speed and flexibility made for only temporary use?
- What would it take for these new concepts and ways of working to become the new and better normal, post-pandemic, in order to reduce drug shortages and accelerate continual improvement and innovation?
- How can trust and an extraordinary level of cooperation among stakeholders continue to be made stronger at a global scale?
- How can scientific advancement, the heightened commitment and common unifying purpose of serving public health, be retained regardless of a pandemic or crisis?
- How can we achieve faster coordination, assimilation, and execution across the globe, instead of countries striving for self-sufficiency and becoming more inward- focused, when solving a global problem?

These and many other questions will continue to arise and persist into the post-pandemic era. It will be essential to use the lessons from this pandemic to prevent and be better prepared for another such pandemic. The past 18 months of the pandemic have

truly tested the pharmaceutical, regulatory and healthcare sectors, as well as governments, societies, countries and communities. Albert Tate, a visionary leader, author and founding pastor of one of the fastest multi-ethnic churches in the US raised a profound question:

> *"What if the COVID-19 pandemic wasn't the test? What if it was the lesson and the test is yet to come on whether or not we will keep these lessons?"*

Building in resilience and a more effective response system to a public health crisis has to be made a priority not only to meet the needs during a crisis, but even outside of it.

10.3 Research Value and Future Research Considerations

The 'wicked' problem of drug shortages and the challenges with slow continual improvement and innovation cannot be resolved overnight through a single set of solutions or by a few stakeholders. As characteristic of a 'wicked problem', there is no way to measure the goodness or effectiveness of any proposed solution. Furthermore, per the 'no stopping rule', no solution to a 'wicked' problem is definitive or final, and solutions cannot be deemed as either good or bad – they simply make the situation better or worse.

The body of work undertaken in this research study was broad, transparent, inclusive, and resulted in the development of several practical science and risk-based standard solutions for both pharmaceutical companies and regulatory authorities that, if implemented across the sector, would deliver regulatory flexibility to enable fast and close to real-time implementation of new knowledge gained through routine operations during the commercial life of a product. The desired objective of the research was a transformational shift where at least 50% of PACs had the potential of being managed within a company's PQS without the need for regulatory prior-approval, whilst still acknowledging that regulatory oversight for those changes was entirely possible, via the inspection and surveillance activities of regulatory authorities.

There are various possible pathways to reduce the global complexity associated with management of PACs. As an illustration developed by the researcher and Vinther, a scenario based on a company making *100* prior-approval PACs globally every month,

and where worldwide approval took an average of *3 years* for each PAC was considered. In this scenario, at any given time the company would be managing *3600* open PACs awaiting regulatory authority approvals. This is a conservative assumption; for global companies, this number is typically much larger. The researcher proposed as shown in Figure 6.1 in Chapter Six of this thesis, two overarching pathways to reduce the global complexity for the faster implementation of these PACs:

1. Increase the use of science and risk basis within the framework of an effective PQS – by implementing the standard solutions described in Chapter Eight of this thesis
2. Increase regulatory reliance – whereby, if one regulatory authority has assessed a PAC or a company's PQS, other regulatory authorities could rely on and accept their conclusions of acceptance or rejection

Building on these pathways, three different mechanisms have been proposed through this research which could assist in reducing complexity and achieving the desired transformation:

1. Mechanism 1 – Reduced approval timelines
2. Mechanism 2 – Regulatory reliance
3. Mechanism 3 – Regulatory flexibility to manage more PACs in the PQS

Figure 10.1 below depicts how these three different mechanisms to reduce complexity could contribute towards achieving the desired transformation; each of these mechanisms is further described following the figure.

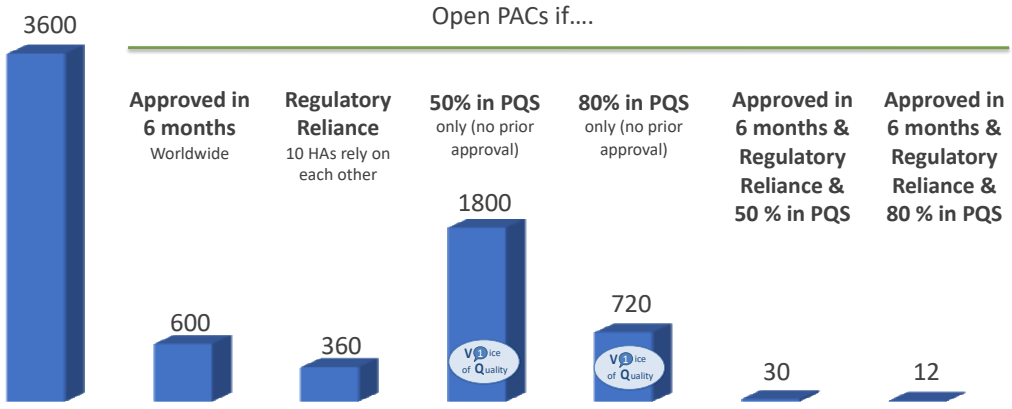

Figure 10.1: Impact of Various Mechanisms to Reduce Global PAC Complexity

The value delivered by each of the three mechanisms or a combination of them as shown in this figure could be described as follows:

- **Mechanism 1 - Reduced approval timelines**: The first mechanism in the figure (bar 2) reflects a reduction in the average time from 3 years to 6 months between first country to last country approval. As depicted, this would reduce the number of concurrently open PACs to 600 (an 83% reduction).
- **Mechanism 2 – Regulatory reliance**: With this second mechanism of regulatory reliance, if regulatory authorities relied more on each other's regulatory assessments of PAC submissions and inspection of their PQSs, doing so would further reduce number of open PACs (bar 3). Assuming 10 regulatory authorities practiced such mutual reliance in this area, this would reduce the number of open PACs down to 360 (a 90% reduction).
- **Mechanism 3 – Regulatory flexibility to manage more PACs within the PQS only**: This third mechanism is the ability to manage and implement more changes within the PQS only, or via a lower change category of regulatory notification, without requiring prior-approval from regulatory authorities, as described in ICH Q10, Annex 1. The fourth and fifth bars in the figure show the reduction that could be achieved if 50% and 80% of the current prior-approval PACs were managed within the PQS only, without having to go through the prior-approval process before implementation. This would reduce the number of open PACs to 1,800 and 720 respectively from the original 3600.
- **Combination of Mechanisms**: Finally, the last bars in the figure show examples of the extent of reduction that is possible through a combination of all 3 mechanisms – reduced approval times, regulatory reliance, and regulatory flexibility per ICH Q10, Annex 1 to handle more changes without prior-approval. This would reduce the number of open PACs to 30 and 12 respectively for the two scenarios, achieving reductions of more than 99% in each case.

Application of all 3 mechanisms individually or in combination, would substantially reduce the overall number of open PACs at any given time and it would lower the extent of global complexity that currently affects PAC management. There has been a recent increase in more NRAs acknowledging the benefits and value of work and resource sharing, and reliance on scientific assessments carried out by other regulatory

authorities. The mutual recognition agreements between EMA and other regulatory authorities like the FDA to rely on each other's GMP inspection system and share information on inspections and quality defects, is an example of this (EMA, 2017). Such reliance can vary by country and be complete, partial (where an NRA still reviews an application but the review is abbreviated or less stringent), or unilateral (where a country decides to rely on the work of another specific trusted NRA). However, as of now, there are very few instances (such as within EU countries,) of mutual reliance for PACs.

This research work has studied and explored ways to reduce the global complexity associated with PAC management; it has developed practical solutions and tools that facilitate regulatory flexibility in this area through enhanced science and risk-based approaches that are grounded in latest product and process knowledge, and where the role of an effective PQS is maximised. The practical solutions presented in this research would allow pharmaceutical companies and regulatory authorities to implement and gain advantage from the application of these possible levers.

PACs are inevitable and essential for maintaining a state of control and for driving continual improvement, as expected by ICH Q10. It is important to make the point that the goal is not simply to reduce the number of PACs, but to facilitate knowledge-led continual improvement when manufacturing and supplying medicines. Reducing the number of PACs that require regulatory approval prior to their implementation, such that the time it takes to implement them is significantly shortened, will drive continual improvement and innovation forward, and at an accelerated pace. This will serve the interests of all stakeholders, but especially patients. Achieving such a transformation via the faster implementation of PACs through unified practical solutions is entirely possible, as concluded by this research, and demonstrated by the rapid action-taking and decision-making during the pandemic by both industry and regulatory authorities. An overall framework for doing so has already been laid out in the ICH guidances - this research work focused on developing practical solutions that would enable those guidances to be implemented and for their vision to be realised. These solutions will enable the faster implementation of new product and process knowledge, thereby advancing continual improvement and innovation, for the ultimate benefit of patients.

If companies and regulators were to implement the solutions presented in this research, then the number of open PACs at any given point in time for a company could be a useful measure of how successful a company has been in the timely management and implementation of new knowledge gained during the commercial life of its products, and in advancing continual improvement and innovation through effective and timely PAC management. It would represent the strength of effectiveness of the company's PQS, including its science and risk-based decision-making. Finally, it would also be a useful indicator of the level of trust and regulatory flexibility earned by the company from regulatory authorities.

Future research areas that could be considered include the following:

- **Development of new *systems thinking-based* solutions including policy and legislation changes:** A deeper exploration into the social, cultural, behavioural and heuristics-related complexity of the problem, through the perspective of stakeholders beyond pharmaceutical companies and regulatory authorities, could lead to the development of additional solutions. Exploring policies at local or regional levels, identifying policies that would be beneficial at global levels, and researching mechanisms to influence and advance such policy development, would contribute further towards meaningful change and impact.

  Calnan in 2014 had identified that a shift from compliance-based quality to excellence-based quality performance, needed a holistic approach to quality and improvement, beyond application of a static set of procedures and GMP-led systems to Total Quality Management (TQM)-based practices (Calnan, 2014). This study affirmed *systems thinking*, as described in Chapter Three, section 3.2.1 of this thesis, as the holistic means to address this complex problem. Additional interconnected solutions need to be designed and implemented within and across interdependent stakeholder groups. This research study established a new stakeholder group of the **CQOs** as the senior-most Quality leaders and decision-makers for the pharmaceutical industry. **PIC/S** is facilitating harmonisation and unification of the global regulatory inspector community. **ICMRA** is starting to unify the global assessor community on this topic through its PQKMS strategic initiative, described in Chapter Six, section 6.5 of this thesis.

There is unprecedented opportunity for these three stakeholder groups to come together in applying *systems thinking* to collectively co-develop standard solutions that will serve the needs of both their individual subsystems and the interfacing, interconnected and interdependent aspects of other subsystems they co-exist with.

- **Progress in innovation and continual improvement**: by exploring how the solutions resulting from this research have impacted the various characteristics of this 'wicked problem' (described in Chapter Four of this thesis). As characteristic of a 'wicked problem', solutions are neither good nor bad – they simply make the situation better or worse. One of the considerations for future research would be exploring whether the solutions resulting from this research have made the current state of continual improvement, innovation and global complexity better or worse, or whether the solutions here have led to any unforeseen consequences.
- **Post-pandemic state:** Learnings that have and are continuing to emerge from the COVID-19 pandemic will provide rich and broad grounds for future research to answer the questions the researcher raised in section 10.2:
    - Why did it take a significant crisis such as COVID-19 to realise the regulatory flexibility and speed that had already been accessible and envisioned for over 15+ years via ICH Q10 and Q9?
    - Why was the applicability of these flexibilities limited to medicines crucial for COVID-19 treatments?
    - Why were these provisions for regulatory speed and flexibility made only temporary?
    - What would it take for these new concepts and ways of working to become the new and better normal, post-pandemic, in order to reduce drug shortages and accelerate continual improvement and innovation?
    - How can trust and an extraordinary level of cooperation among stakeholders continue to be made stronger at a global scale?
    - How can scientific advancement, the heightened commitment and common unifying purpose of serving public health, be retained regardless of a pandemic or crisis?

- How can we achieve faster coordination, assimilation, and execution across the globe, instead of countries striving for self-sufficiency and becoming more inward-focused in solving a global problem that afflicted every nation?

- **Advancing regulatory reliance:** While this research has identified regulatory reliance as an essential component in resolving the 'wicked problem' of drug shortages, exploring the current state of regulatory reliance or mechanisms, and bringing regulatory authorities together to advance global regulatory reliance could be a valuable topic for future research. Particular focus on non-ICH regions or countries, their regulatory systems, infrastructure, challenges and opportunities, could further expand understanding of the problem and the possibilities for other potential solutions.

  At the time of this thesis submission, a new Ph.D. research study at PRST in TU Dublin has been approved for V. Sachdeva; titled '**Facilitating reliance approaches through collaborative registration procedure (CRP): How National Medicines Regulatory Authorities (NMRAs) can expedite Marketing Authorisation and Post-approval Changes (PACs) to ensure timely and uninterrupted supply of the medicinal products.'**

  This future research study intends to further facilitate a reduction in PAC implementation timelines by:

  - Influencing greater harmonisation and coordination of actions from individual countries by working with NMRAs that are in the most mature cohort and facilitating the sharing of good practices
  - Providing capability and maturity building supporting materials (training, case studies, reference examples) for NMRAs and by encouraging more convergence regarding the management of the PAC process through global regulatory bodies such as PIC/S

Innovation is necessary not only for new medicines but also for medicines that are already on the market and will remain so for years, maybe decades.

The three years of this research study, preceded by almost five years of pre-research foundational work, and now being followed on by the future research referred to above,

underlines the importance, need and value of continual improvement and innovation for patients and public health. As long as patients are waiting for their medicines, we cannot be good enough or fast enough – the journey of doing more and better must continue.

10.4 Additional Post-Research Reflections

At the conclusion of this research study, as the researcher circled back to the approved 2005 Business Plan for ICH Q10 and the envisioned benefits, she and Vinther sent a short survey to the 30 CQOs on 1-Sept-2021, 13 years after the PQS model in ICH Q10 was published, asking the following question:

Since 2008, on a scale of 1-5, how much do you think each of the potential benefits (A through E below) envisioned for ICH 10 have materialised in your daily operations in your current and/or previous companies?

1 = Things have become significantly worse or complex

2 = Things have become slightly worse or complex

3 = No change

4 = Things have improved slightly (less complex)

5 = Things have improved significantly (less complex)

Table 10.1 below provides an average of the 10 CQOs that responded:

Table 10.1: Survey of CQOs on the Extent of ICH Q10 Benefits Realisation

Envisioned Benefit	Score Range	Average Score
Improved process performance	2 - 4	3.44
A reduction in the costs of internal failures (rejects, reworks, reprocessing and investigations) as the quality system guideline drives improvement	2 - 4	3.11
A reduction in the costs of holding duplicate stock and operating multiple processes as improvements and changes are made more effectively across all regions	1-3	2.44
A reduction in the costs of preparing / reviewing certain regulatory submissions	2-3	2.33
Enhanced assurance of consistent availability to the patient	2-4	2.78

The responses from these Senior Quality Leaders were disappointing in that they indicated ICH Q10 has not had much positive impact at all – the responses were mostly that it had made no change, and in several instances had made the situation slightly worse or more complex. Some comments provided below convey further context behind these scores:

- *"I think higher expectations have not driven better process design beyond what we should have been doing in the first place – CPV maybe tells you when things aren't right but that's after the fact."*
- *"I see no change in failures due to Q10 as we always strive to get to root cause and decent CAPAs so have reduced deviations because of good investigations. QRM is an added workload to little impact from what I have seen. What you don't know you still don't know."*
- *"Supply chain complexity driven by different regulators has only made things worse."*
- *"Our world has got more complex and Q10 didn't help for anything."*
- *"While the PQS is helpful, the complexity of the regulatory framework has actually prevented the last three potential benefits".*
- *"The fact that I have to respond as I do is disappointing."*
- *"The consensus is that ICH Q10 did not have a significant impact on daily operations at our company as we already had a strong PQS. Since the introduction of Q10 in 2008, we have undergone several Enterprise initiatives which were focused on driving further standardization across the breadth of the company's Business Segments including medical device, pharmaceutical and consumer health. While we have implemented many changes since the introduction of Q10 in 2008, none of these changes were specifically driven by or linked to Q10. With regard to regulatory submissions, ICH Q8(R2), Q9, Q11 and now Q12 have had more impact. Although aligned with these other ICH guidance documents, ICH Q10 has not significantly impacted the regulatory submission process. Q10 does provide benefit in terms of globally harmonized definitions and expectations when working with 3rd parties."*

This led the researcher to a useful post-research reflection, linking the nature and complexity of a 'wicked problem', the body of work and outcomes from this research study, the unexpected insights from the COVID-19 pandemic – that standard solutions developed and implemented in a collaborative, unified manner within and across interdependent stakeholder groups, has likely been the missing component for realisation of the desired state and benefits envisioned by ICH Q10, Q9 and now ICH Q12. Solving a 'wicked problem' requires *systems thinking*, as uncovered by this research study. Harmonising on concepts and high-level approaches is an important step, but it might only be the first step in the journey to the desired state – standard solutions are necessary. ISO standards and standard ISO certifications provide a useful

paradigm that the pharmaceutical sector might need to consider. Time and the extent of consistent and unified adoption will tell how the solutions resulting from this research study influence the achievement of the potential benefits envisioned above, whether or not they accelerate the pace of continual improvement and innovation in the pharmaceutical sector, and whether or not this ultimately leads to a marked reduction in drug shortages. This research study's recognition that the pharmaceutical, regulatory, healthcare, legislative and governmental sectors must operate as a dynamic adaptive 'living system' to open up numerous opportunities for these stakeholders to rise above their organisational boundaries, limitations and assumptions and create new pathways for interacting and collaborating, ways that will transform their service of public health.

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Appendices

Appendix I: Researcher's Prior Experience

Appendix I summarises the researcher's professional career experience in the pharmaceutical industry, her role and involvement in establishing a QRM programme at the company of employment Roche/Genentech, her activities in advancing risk-based application both for the company and broader for the pharmaceutical industry, and how these led to her extensive industry work and the current research study into Drug Shortages and PAC Management. Drug shortages and integration of QRM into the PQS, are the specific areas of the researcher's risk-based application experience discussed in this appendix.

Significant Publications Underpinning this Research

It is useful to follow the researcher's journey by reviewing the timeline of significant publications underpinning this research. Figure 2.2 in Chapter Two *(Literature Review)* provides a timeline-based overview of key publications relevant to this research; highlights from the researcher's career, leadership and publication experience starting in 2003 till date, are mapped against it. The figure is organised to show on the left side, the guidelines that informed this research. These are mainly the ICH guidelines – ICH Q8 (R2), Q9, Q10 and Q11, and the PIC/S Recommendation Paper on demonstrating effectiveness of risk-based change management (PIC/S, 2019). The far right of the figure highlighted the researcher's key leadership and publications experience that are relevant for this research. Chapter Two discussed the specifics of the ICH guidelines that underpinned this research.

Researcher's Career Experience Informing this Research, Prior Registration Research Work

Figure 2.2 in Chapter Two laid out the researcher's career experience, and her leadership and influencing experience in the pharmaceutical industry, with regulators, and via the PDA. This section gives a high-level review of the researcher's career prior to registration for this Ph.D. Following this, specific details relating to QRM, drug shortages, and PACs will be discussed.

The researcher's career commenced with QRM practical implementation experience in 2003, with foundational QRM concepts for medical device combination products first, and then for pharmaceutical and biotechnological products. QMS and QRM application for medical devices based on ISO concepts, started in 1996 with the publication of the first ISO 13485 standard, *Medical Devices* (intended for the design, production, installation and servicing of medical devices and related services), latest revision being ISO 13485:2016 (ISO, 2016); and in 2000, the first ISO 14971 standard, *Medical Devices – Application of Risk Management to Medical Devices* (that specifies the terminology, principles and a process for risk management of medical devices through all phases of a device's lifecycle), latest revision being ISO 14971:2019 (ISO, 2019). Due to these ISO standards, the medical device industry has a longer history and higher maturity with QMS and QRM integration into device lifecycle management, than the pharmaceutical or biotechnology industry, which did not have the ICH Q9 and ICH Q10 guidance until 2005 and 2008, respectively. Hence, gaining operational experience with device combination products was very beneficial, as it afforded the researcher with a knowledge of device Quality System Regulations and integrated QRM application into device lifecycle management, as expected by ISO 13485 and ISO 14971.

This foundational experience in device QRM and device QMS was then expanded in 2005 when the researcher made a career change towards pharmaceutical and biotechnological products. This was also when ICH Q9 was published followed by ICH Q10, a few years later in 2008. During her role in the Corporate Quality System and Support function at Genentech, the researcher gained experience with design and implementation of a PQS per ICH Q10 expectations. This was followed by gaining practical experience on QRM application per ICH Q9 for pharmaceutical and biotechnology products and processes - first as the Global Head of Quality Risk Management for Genentech starting in 2008, and then for Roche through 2012, the researcher was responsible for the design, deployment, and governance of a harmonised QRM programme (global standards, business processes, global tools including an IT tool, templates and role-based QRM training) across both companies. In addition, the researcher acted extensively as a QRM facilitator and trainer, led complex cross-functional, cross-site risk assessments, led complex network-wide QRM strategies for products, processes and systems, including risk-based regulatory filings, and led the

integration of QRM into end-to-end product management and into the PQS, within the Roche/Genentech organisation.

The researcher has been a member of PDA since 2002, and has actively volunteered for a range of technical, quality and regulatory topics. While she was leading QRM implementation at Roche/Genentech, in December 2008, PDA established an initiative known as the Paradigm Change in Manufacturing Operations (PCMO®). The goal of this initiative was to establish 'best practice' documents and/or training events that would assist pharmaceutical manufacturers in implementing ICH Q8, Q9, and Q10 guidelines. The strategic objectives of PCMO® were as follows:

- Enable an innovative environment for continual improvement of products and systems,
- Integrate science and technology into manufacturing practice,
- Enhance manufacturing process robustness, risk-based decision making and knowledge management, and
- Foster communication among industry and regulators.

The researcher was invited to lead the QRM workstream under the scope of the PCMO® programme. This involved leading a Task Force for the development of the parent Technical Report 54 and sub-teams that developed QRM application case studies.

In parallel, during this part of her career journey, the researcher became increasingly involved in QRM interactions and dialogue within the larger pharmaceutical industry through training programmes, workshops, conferences, and interactions with regulators across different regulatory authorities including the FDA, EMA, HPRA and Health Canada, among others.

These external interactions beyond her role at Roche/Genentech, allowed the researcher to broaden her pharmaceutical industry leadership and influence of QRM practices including training regulatory authorities (FDA, EMA, Health Canada, PIC/S) on QRM applications, and how to review or inspect risk-based applications. Figure 2.3 in Chapter Two highlights key aspects of the researcher’s experience with training programmes, workshops, and influencing the pharmaceutical industry and regulators on QRM implementation and applications.

In 2012, the researcher changed roles and assumed responsibilities as the Head of Global Biologics QC, Roche/Genentech, with a further specialised broadening in 2018 as the Global Head of Analytical Science and Technology for both Biologics and Small Molecules. In these roles, the researcher's focus was analytical control systems lifecycle management and product lifecycle management. Relevant to this research, the researcher integrated QRM application into the lifecycle management decisions for product analytical control systems. It became adequately evident during this part of her work that the restricted ability to make PACs to analytical methods, specifications and product controls (due to the significant global complexity), even when latest product and process knowledge indicated a need for change, could indirectly contribute to drug shortages, as described in PDA Technical Report 68. During this period drug shortages were rapidly becoming an increasing global concern both for regulators and pharmaceutical companies.

Therefore, compelled by the need and importance of reducing drug shortages, one of the areas of risk-based application that the researcher expanded her work into starting in 2012 through 2015, was risk-based prevention and management of drug shortages. Extensive discussions within the pharmaceutical industry and with regulators, particularly EMA and FDA, and her real-time experience with long lead times for global implementation of PACs for analytical methods/technologies, directed the researcher's exploration into the global complexities of PAC management, and how extended approval timelines for a change might contribute to worsening the global drug shortages problem.

In 2012 the researcher took on leadership for the development of Technical Report 68 on a Risk-Based Approach for Prevention and Management of Drug Shortages. This report provides practical application, a Risk Triage model and templates for both proactively preventing and responding to drug shortages, as described in Chapter Five, section 5.3.4 (Ramnarine *et al.*, 2014). In addition, the researcher functioned as the PDA co-lead on EMA's Inter-association Task Force that was established as a result of European Commission's Call to Action in 2012 (European Commission, 2012). During this time, the researcher also led drug shortage workshops, training sessions, and delivered several relevant presentations; a list of all these are given in Figures 2.2 and

2.3. This body of work on drug shortages and the EMA Inter-Association Drug Shortages Task Force, is described in further detail in Chapter Five.

Once the final report and recommendations from the EMA Drug Shortages Inter-Association Task Force was completed and submitted to the EMA, the researcher directed her focus to one of the potential factors that had started to surface during the course of her work on drug shortages – *the enormous global complexity of PAC management*. In 2015, the researcher proposed to PDA the importance and need of initiating dialogue with the pharmaceutical industry and regulators on the challenges with PAC Management.

The PDA Board of Directors approved the establishment of a Post-Approval Change: Innovation for Availability of Medicines (PAC iAM^{SM}) Task Force in 2016 with the researcher as a co-lead. This Task Force brought together leaders from different pharmaceutical companies, and their work led to the development of several articles, presentations and papers which are discussed previously in Chapter Seven, section 7.1 of this thesis; these papers also became sources of input to the ICH Q12 EWG as they developed the content for ICH Q12.

During the course of this work and through a meeting with Dr Janet Woodcock described in Chapter One, the PAC iAM^{SM} Task Force's work was expanded in 2018 to become a platform to enable and establish a unified pharmaceutical industry position on Quality topics relevant to PAC Management – this became the *1VQ for PAC Initiative* under the co-leadership of the researcher and is described in detail in Chapter Seven of this thesis. A high-level overview of the PAC iAM^{SM} Task Force and the initial *1VQ for PAC* activities is presented in a diagram developed by the researcher shown in Figure AI-1 below.

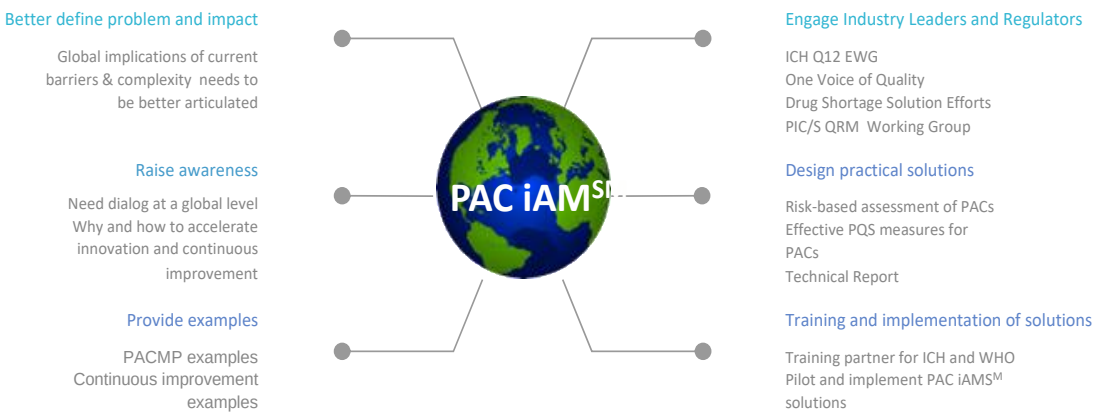

Figure AI-1: Researcher's Scope of Work for PAC Management

Beyond active leadership on the topics of QRM, Drug Shortages and PAC Management, the researcher has served on the PDA's Board of Directors since 2014, is currently the Secretary of the PDA Board Executive Committee, and was on PDA's Regulatory Affairs and Quality Advisory Board (RAQAB) from 2013 through 2019.

Her collective global pharmaceutical industry experience and thought leadership over 16+ years prior to registration in this PhD research programme, forms a strong basis for this research study. The researcher pre-registration body of work for QRM, drug shortages and PAC management became a relevant basis as she continued this research study with a deeper academically structured focus. The researcher is keenly driven not only by her interest in these topics, but more importantly her passion for making a difference for patients and public health - by advancing the pharmaceutical industry and enabling opportunities for collaborations with regulatory authorities to develop and implement joint solutions that will contribute towards solving complex problems through practical application of science and risk-based approaches.

The following sub-sections provide a breakdown with further details on the researcher's prior-registration QRM, drug shortages and PAC management experience.

Researcher's QRM Experience

From 2012-2017, the researcher co-led PDA's QRM Interest Group (QRM IG) which grew in membership during the course of her leadership term to greater than 600 members. The QRM IG became one of PDA's most active IGs for grass-roots

exchange, dialogue, collective learning and exchange across companies, sharing practices on QRM programme design and implementations within companies, and therefore overall contributing to elevating the industry's maturity in QRM use and practice. The researcher's QRM -related leadership experience is listed in Table AI-1.

Table AI-1: QRM-Related PDA Leadership Experience

- PDA Task Force Leader for **Technical Report 54: Implementation of Quality Risk Management for Commercial and Biotech Manufacturing Operations,** 2009-2012.
- Lead **PDA's Paradigm Change in Manufacturing Operations (PCMO®) Risk-based Manufacturing Task Force**, 2010-2012.
- Co-chair of **PDA Quality Risk Management Interest Group**, 2012-2017.

The researcher ensured that Technical Report 54 **"Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations"**, which was the first Technical Report to be published in March 2012, under PDA's PCMO® initiative (Ramnarine *et al.*, 2012), was developed such that it was practical and could be applied by all companies regardless of their size or infrastructure. This technical report was also the basis for the subsequent series of technical reports on QRM application case studies as depicted in Figure AI-2.

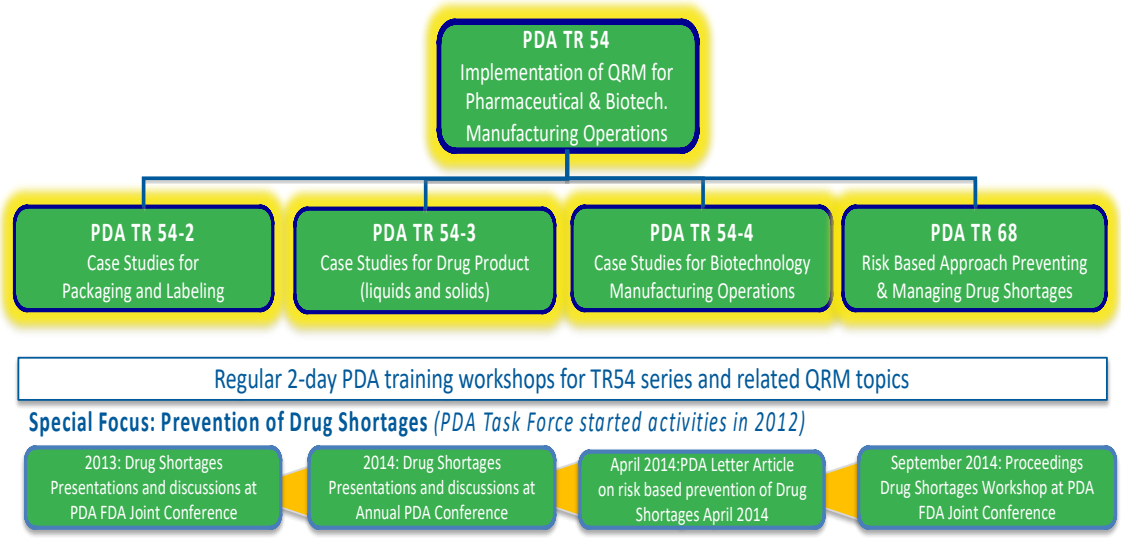

Figure AI-2: QRM Related Technical Reports

In addition to the technical reports, the researcher was also actively involved in a benchmarking survey on the pharmaceutical industry's QRM maturity (Waldron,

Ramnarine and Hartman, 2017), led by Dr Kelly Waldron and supported by the researcher (in her capacity as the PDA QRM IG Leader). Details of the researcher's QRM publication experience resulting from the leadership of PDA Quality Risk Management Technical Report 54 Task Force and the QRM IG is listed in Table AI-2.

Table AI-2: QRM Publications

1. A. Mire-Sluis, E, Ramnarine, J. Siemiatkoski et.al., **Practical Applications of Quality Risk Management**, BioProcess International, March 2010.
2. E. Ramnarine, J. Hartman, L. Huffman et. al. **Implementation of Quality Risk Management for Pharmaceutical and Biotech Manufacturing Operations,** PDA Technical Report 54, 2012.
3. E. Ramnarine, **Understanding Problems of Subjectivity and Uncertainty in Quality Risk Management, Quality Risk Management in the GMP Environment – Ten Years Since the Finalisation of ICH Q9 – A Critical Review** 2005-2015, The Journal of Validation Technology – 10 Year Anniversary Special Edition, December 21, 2015, 43-50.
4. K. Waldron, E. Ramnarine. J. Hartman, 2016/2016 **Quality Risk Management Benchmarking Survey**, PDA Journal of Pharmaceutical Science and Technology, 71 (2017): 330-345.

In addition to the activities discussed above, the researcher developed and delivered several QRM training and workshop sessions for the pharmaceutical industry and regulators as part of PDA and beyond PDA. Given the pharmaceutical industry's lower QRM maturity, the researcher set in motion with PDA Training and Research Institute (TRI), another activity related to the development and implementation of PDA's Role-based modular QRM Training and Certification Programme. The researcher led the conceptual creation of this modular role-based certification program, which is further helping raise industry's application and maturity with quality risk management. The researcher's experience in designing and delivering quality risk management training sessions and workshops is listed in Table AI-3, with the ones highlighted in blue, being training programmes and workshops provided to regulators.

Table AI-3: QRM Training and Workshop Experience

- E. Ramnarine as Head of Genentech-Roche Global Quality Risk Management, established Genentech & Roche's QRM program, 2009-2012.
- E. Ramnarine as Head of Genentech-Roche Global Quality Risk Management, **QRM Training for Investigators**, 2009.
- E. Ramnarine, Risk Assessment Fish Bowl, WCBP CMC Strategy Forum, Practical Applications of Quality Risk Management, July 27-28 2009, NIH Bethesda. On Planning Committee for the 2-day Forum (125 regulators from 33 global regulatory authorities).
- E. Ramnarine, V. Davoust, **Quality Risk Management in Manufacturing**, *PDA Training and Workshop*, May 6-7, 2011, London.

- E. Ramnarine, **The Benefit of QRM Methodology Case Study: Integrating Quality Risk Management During Technology Transfer**, *PDA Training and Workshop*, May 6-7, 2011, London
- E. Ramnarine, **Integration of Quality Risk Management into The Quality System**, *PDA Training and Workshop*, May 6-7, 2011, London.
- E. Ramnarine as Head of Genentech-Roche Global Quality Risk Management, **Auditing QRM Training for Auditors**, 2011.
- E. Ramnarine as Head of Genentech-Roche Global Quality Risk Management, **Modular Role-Based QRM Training Program for QRM Facilitators, QRM Lead, Decision Makers and QRM Participants/Subject Matter Experts** (includes modules on QRM process steps and different QRM tools), 2008-2012.
- E. Ramnarine, K. Terry, A. Mire-Sluis, D. Weese, K. Murray, S. Reich, R. Spohn, **FDA 2-day QRM Workshop**, January 20-21, 2011, NIH Bethesda (trained 50+ regulators).
- E. Ramnarine, K. Terry, A. Mire-Sluis, D. Weese, K. Murray, S. Reich, R. Spohn, **Health Canada 2-day QRM Training**, June 16-17, 2011, Ottawa (trained 70+ regulators).
- E. Ramnarine, K. Terry, L. Richter, R. Spohn, **Advanced FDA 2-day QRM Workshop**, November 3-4, 2011, NIH Bethesda (trained 100+ regulators).
- E. Ramnarine, J. Hartman, **Implementation of Quality Risk Management for Pharmaceutical and Biotech Manufacturing Operations, PDA TR54 Training (**2-day), April 2012. Delivered multiple training sessions (trained 100+ attendees).
- E. Ramnarine, **Understanding Risk Management Fundamentals for Data Integrity – Why Does it Matter?** *2015 Data Integrity Training Workshops with FDA and CFDA*, August 28-September 4, 2015, Beijing, Nanjing, Hangzhou (trained 350+ attendees from China industry and CFDA).
- E. Ramnarine, **Practical Application of Quality Risk Management for Data Integrity**, *2015 Data Integrity Training Workshops with FDA and CFDA*, August 28-September 4, 2015, Beijing, Nanging, Hangzhou (trained 350+ attendees from China industry and CFDA).
- E. Ramnarine, **Understanding the Problems of Subjectivity and Uncertainty in QRM – Issues to Consider**, *PIC/S QRM Expert Circle Training, Use of Advanced QRM by Regulatory Agencies*, Sept 26-28, 2015, London (trained 75+ regulators from 15 countries).
- E. Ramnarine, **Understanding the Problems of Subjectivity and Uncertainty in QRM – Issues to Consider**, US *PIC/S QRM Training Event*, October 5-7, 2015, Los Angeles. (trained 80 regulators from 15 countries).
- E. Ramnarine, **Understanding the Problems of Subjectivity and Uncertainty in QRM – Issues to Consider**, *PIC/S QRM Training Workshop*, September 11-13, 2018, Taipei (trained 68 regulators from 16 countries).
- E. Ramnarine, S. Ko, **Gain Proficiency in Quality Risk Management: PDA's New Role-based QRM Certificate Program Offers Courses for all Levels of QRM Involvement**, October 2017. https://www.pda.org/pda-europe/news-archive/full-story/2017/10/03/gain-proficiency-in-quality-risk-management. Led the design, development and implementation of the role-based modular training and Certificate Program.
- E. Ramnarine, G. Claycamp, A. McFarland, **Quality Risk Management: Risk Control and Risk-based Decision-Making** Training as part of *PDA's QRM Certificate Program*, December 2017. Delivered multiple training sessions.

In addition to the training and workshop activities listed above, the researcher also gave QRM presentations at various conferences as listed in Table AI-4.

Table AI-4: QRM Presentation Experience

- E. Ramnarine, **A Harmonized Risk-based Validation Approach for Manufacturing and Computer Systems**, *2009 Annual PDA Conference*, April 20-22, 2009, Las Vegas.
- E. Ramnarine, **Integration of Quality Risk Management into the Quality System – Operationalizing QRM**, *2009 PDA/FDA Joint Regulatory Conference*, September 2009, Washington DC.
- J. Edwards, E. Ramnarine, B. Rellahan (FDA), N. Waites (FDA), **Implementation of Quality Risk Management – Challenges and Considerations for Biopharmaceuticals**, *WCBP CMC Strategy Forum*, January 25-27, 2010, Bethesda.
- E. Ramnarine, **Practical Applications of Quality Risk Management as an 'Enabler' of the Quality System**, *GMP by the Sea*, August 16-18, 2010, Savannah.
- E. Ramnarine, **Quality Risk Management in Manufacturing**, *2010 PDA/FDA Joint Regulatory Conference*, September 15, 2010, Washington DC.
- E. Ramnarine, **Quality Risk Management in Manufacturing**, *2011 PDA/FDA Joint Regulatory Conference*, September 19-21, 2011, Washington DC.
- E. Ramnarine, **Implementation of Quality Risk Management at Roche, PDA West Coast Professional Dinner Meeting Series**, September 29, 2011, San Francisco.
- E. Ramnarine, **Practical Implementation of Quality Risk Management**, *2011 Annual ISPE Conference*, October 5, 2011, Boston.
- E. Ramnarine, **Quality Risk Management in Technical Research and Development**, *ISPE QRM Working Group*, August 19, 2013, Washington DC.
- E. Ramnarine, **Hammer or Screwdriver? Practical Applications of QRM Tools and The Formality Spectrum**, *PDA/FDA ICH Q10 Workshop on Quality Risk Management*, November 3-5, 2015, Maryland.
- E. Ramnarine, Integration of QRM Into The Quality System, *FDA Quality Systems Work Group*, December 11, 2015, FDA Bethesda.

Researcher's Drug Shortage Experience

In 2012, the researcher focused on the topic of drug shortages as EMA and FDA heightened their attention to this growing global concern. This focus was in particular on practical risk-based applications such that the risk and/or impact of drug shortages could be proactively assessed, and the risk control actions needed to prevent, or mitigations needed to respond to drug shortages, were commensurate with the level of risk.

In 2012, PDA established a Drug Shortage Task Force as part of the PCMO® programme under the leadership of the researcher, who led it through 2015 as noted in Table 1. This was a continuation of PDA's Technical Report No. 54 series of documents on quality risk management application case studies. The Drug Shortage

Task Force published PDA Technical Report 68 (Ramnarine *et al.*, 2014), as described in Chapter Five, section 5.3.4 of this thesis.

Table AI-5 lists the researcher's Task Force leadership experience related to Drug Shortages.

Table AI-5: Drug Shortages Task Force Leadership Experience

- PDA Task Force Leader for **Technical Report 68: Risk-based Approach for Prevention and Management of Drug Shortages**, 2012-2014.
- PDA Co-Lead for **EMA Inter-association Task Force on Drug Shortages.** Led the development of PDA's risk-based approach, tools and templates for drug shortage prevention and response plan. 2013-2015**.**

Drug shortages related publications during the course of the researcher's leadership of the PDA Drug Shortage Task Force and being on the EMA Inter-association Task Force are provided in Table AI-6.

Table AI-6: Drug Shortages Publications

- E. Ramnarine, S. Rönninger, A. Vinther, **Preventing and Managing Drug Shortages**, *PDA Letter*, April, 2014, 36-39.
- E. Ramnarine, A. Vinther et.al. **Risk-Based Approach for Prevention and Management of Drug Shortages**, PDA Technical Report 68, 2014
- **Prevention of Drug Shortages Based on Quality and Manufacturing Issues**, Interim Report to EMA on a Collaborative Contribution to the EMA and their Inspectors Working Group (EMA-IWG), November 18, 2014. Report authored by ISPE, PDA, EFPIA, EGA, AESGP and PPTA. [PDA Authors E. Ramanarine, A. Vinther].
- E. Ramnarine, M. Jornitz, M. A. Long, K. O'Donnell (HPRA), S. Rönninger, C. Smalley, A. Vinther, **Risk-based Approach for Prevention and Management of Drug Shortages**, *PDA Technical Report 68*, 2014.
    - Included in European Medicines Agency's (EMA) Final Report on a Collaborative Contribution to the EMA and their Inspectors Working Group (EMA-IWG) on Prevention of Drug Shortages based on Quality and Manufacturing Issues, 23, December 2014, 9-11. https://www.pda.org/docs/default-source/website-document-library/scientific-and-regulatory-affairs/drug-shortage/interrupted-supply-inter-association-summary-final-report-2014.pdf?sfvrsn=4

In addition to leading the PDA Task Forces, the researcher chaired a workshop on drug shortages in 2014 and delivered several training programmes as listed in Table AI-7, while also representing PDA in the Inter-Association Task Force that was established in 2013 at the request of EMA. An overview of PDA's 2014 drug shortages workshop, and

the body of work related to EMA's Inter-Association Task Force is provided in Chapter Five, section 5.3.

Table AI-7: Drug Shortages Workshop and Training Experience

- PDA Drug Shortages Workshop, September 10-11, 2014. Workshop Chair.
- E. Ramnarine, A. Vinther, S. Rönninger, **Risk-based Prevention and Management of Drug Shortages, PDA TR68 Training** (1-day), July 2015. Delivered multiple training sessions (trained 40+ attendees).
- E. Ramnarine, A. Vinther, S. Rönninger, G. Roessling, **PDA's Risk-based Prevention and Management of Drug Shortages**, *EMA Drug Shortage Workshop*, October 9, 2015, London.

The researcher further delivered several presentations on risk-based application for drug shortages at various conferences and discussion forums involving pharmaceutical companies and regulators. This body of work is listed in Table AI-8

Table AI-8: Drug Shortages Presentation Experience

- E. Ramnarine, **Risk and Knowledge Management Leading to Robust Manufacturing Process Control**, *2012 PDA/FDA Joint Regulatory Conference*, September 10-12, 2012, Baltimore
- E. Ramnarine, **Risk-based Approach to Manage Drug Shortages**, *PDA/FDA Joint Regulatory Conference*, Sept 2013, Washington DC.
- A. Vinther, E. Ramnarine, **PDA Risk-based Approach to Prevent and Manage Drug Shortages**, *EMA Drug Shortage Meeting with Interested Parties*, November 26, 2013, London.
- A. Vinther, E. Ramnarine, **PDA Risk-based Approach to Prevent and Manage Drug Shortages**, *EMA Drug Shortage Meeting*, January 27, 2014. London.
- E. Ramnarine, **PDA Risk-based Approach to Manage Drug Shortages. Inter-Association Drug Shortage Prevention Initiative with EMA,** *ISPE Annual European Conference*, April 29-30 2014, Frankfurt.
- E. Ramnarine, **Preventing and Managing Drug Shortages**, *2014 PDA/FDA Joint Regulatory Conference*, September 8, 2014, Washington DC.
- E. Ramnarine, A. Vinther, S. Rönninger, G. Roessling, **PDA's Risk-based Prevention of Drug Shortages Update,** *EMA Drug Shortages Inter-Association Task Force Meeting*, September 22, 2014, Brussels.
- E. Ramnarine, A. Vinther, S. Rönninger, G. Roessling, **PDA's Risk-based Prevention of Drug Shortages Update,** *EMA Meeting*, October 2, 2014, London.
- E. Ramnarine, **TR68: Risk-based Prevention and Management of Drug Shortages. How Companies Can Implement a Practical Approach**, *PDA Midwest Chapter*, March 15, 2015.
- E. Ramnarine, **TR68: Risk-based Prevention and Management of Drug Shortages. How Companies Can Implement a Practical Approach**, *2015 Annual PDA Conference*, March 16-18, 2015, Las Vegas.
- E. Ramnarine, **Technical Report 68: Risk-based Approach for Prevention and Management of Drug Shortages**, *2015 PDA/FDA Joint Regulatory Conference*, September 28-30, 2015, Washington DC.
- E. Ramnarine, **Post Approval Change and Knowledge Management. Where are We? Results**

from the PAC iAM Task Force Survey, *2017 PDA Annual Meeting*, April 3-5, 2017 Anaheim**.**

- E. Ramnarine, S. Rönninger**, Managing Single- and Multi-Source Supply Chain Challenges. A Practical Tool for Prevention and Management of Drug Shortages,** *2nd Annual PDA Europe Conference*, June 13-14, 2017, Berlin.

Researcher's PAC Management Experience

As described in Chapter One, the causes of drug shortages are complex and multi-factorial, with one of the many causes being manufacturing and quality issues (Birgli®, 2013). As part of this research and work on drug shortages, and development of Technical Report 68: *Risk-Based Prevention and Management of Drug Shortages*, the researcher started exploring the topic of long PAC timelines across many regulatory authorities that need to approve a change before it can be implemented (Ramnarine *et al.*, 2014). The researcher initiated a discussion on how drug shortages could potentially be reduced through expedited PAC management.

PAC management remained the current focus of the researcher's work that started in 2016, and extended into this doctoral research. This research is intended to study solutions that could transform PAC management even with the currently highly diverse and complex global regulatory landscape, in order to ensure timely availability of much-needed medicines for patients. Figure AI-3 provides an overarching summary of the researcher's prior scope of work with PDA for PAC management, and her direct involvement and influencing efforts for PAC management activities.

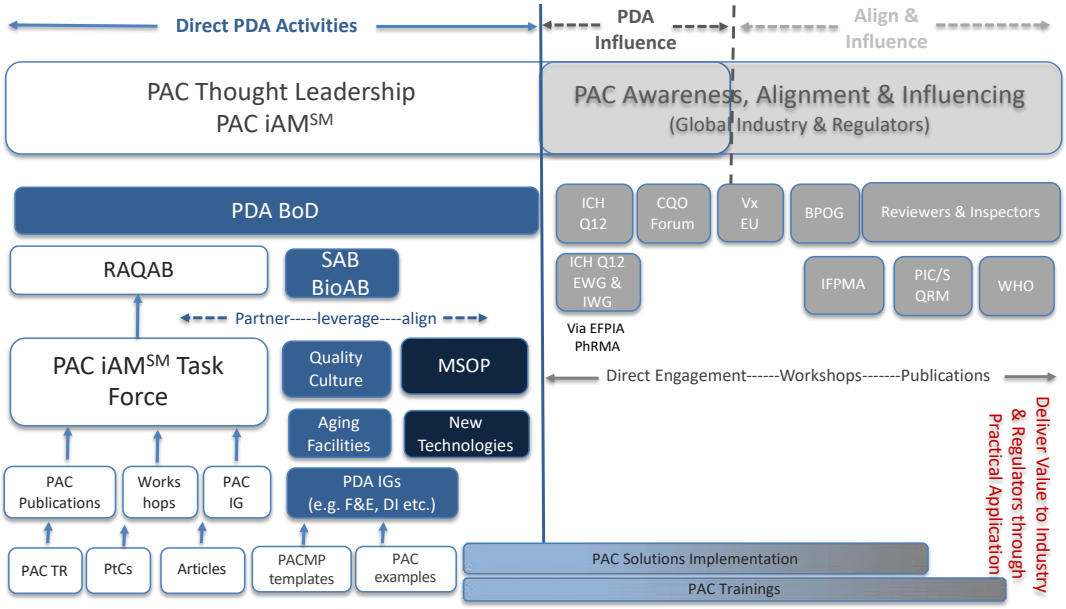

Figure AI-3: Researcher's Involvement (Direct and Influencing) in PAC Management

Table AI-9 lists the researcher's PAC management leadership experience.

Table AI-9: PAC Management Industry Task Force Leadership Experience

- PDA Co-Lead for **Post Approval Change Innovation for Availability of Medicine (PAC iAM^SM) Task Force**, 2016-2018.
- Co-Lead for Industry One-Voice-of-Quality (1VQ) on Post-Approval Change Management, 2018-Present

Details of the activities including workshops and focus groups conducted as part of the researcher's PAC leadership are the subject of this research and described in this thesis. The researcher's key presentations on PAC management prior to initiating this research study are listed in Table AI-10.

Table AI-10: PAC Management Presentation Experience

- M. James, E. Ramnarine, A. Vinther, **Lifecycle Management, PDA and GSK Input to ICH Q12 Lifecycle Strategy**, November 25, 2015 & May 4, 2016.
- E. Ramnarine, A. Vinther, U. Busse**, Post Approval Changes: The Need and Concept of Global Change Protocols**, Presentation to the PDA *Manufacturing Science and Operations Program*, June 22, 2016.
- E. Ramnarine, Analytical Control System Lifecycle Management, *1st Annual PDA Europe Conference*, June 28-29, 2016, Berlin
- E. Ramnarine, A. Vinther, M. Seymour, D. Baker, **FDANews Webinar – PDA's Post Approval**

Change: Innovation for Availability of Medicines Program, February 8, 2017. http://info.fdanews.com/pdas-post-approval-change-innovation; https://www.pda.org/docs/default-source/website-document-library/workshops/2017/pac-iam/fda-news-webinar.pdf

- E. Ramnarine, A. Vinther, M. Seymour, **Q1 Productions Webinar - Lifecycle Management: Update and Insights on Post Approval Changes and PAC iAM Activities**, July 25, 2017.
- E. Ramnarine, **Product Lifecycle Management**, *PDA PAC iAM Workshop*, September 13-14, 2017, Washington DC.
- E. Ramnarine, **Post Approval Change and Product Lifecycle Management**, *PDA West Coast Chapter Meeting*, February 22, 2018.
- E. Ramnarine, **Risk-based Post Approval Change and Lifecycle Management**, *ECA Quality Risk Management Summit*, June 20-21, 2018, Lisbon.
- E. Ramnarine, U. Busse, **ICH Q12 and Post Approval Change: PDA Innovation for Availability of Medicines**, *3rd Annual PDA Europe Conference*, June, 2018, Berlin.
- E. Ramnarine, **How Can We Foster an Environment With An Incentive For Industry To Continually Improve And Reduce Risk To Patient?** *PIC/S QRM Expert Circle Meeting*, September 13, 2018, Taiwan.

The researcher's prior work on the topics of QRM, drug shortages, and PAC management, activated extensive dialogue in the pharmaceutical industry on these topics, and has helped pharmaceutical companies come together in sharing their experiences, learnings and working together to move forward in their risk-based application maturity. It also helped increased awareness of regulators to the global complexities associated with the diverse regulatory expectations across different regulatory authorities. This in turn advanced the dialogue between the pharmaceutical industry and regulators through different forums on understanding mutual challenges and a recognition and appreciation that no single stakeholder group can solve these complex problems of drug shortages and PACs on their own.

The researcher's prior work described in this Appendix I laid important groundwork for this PhD research study.

Appendix II: Index to Study-related Publications, Proposals to Regulatory Authorities and Key Presentations

This appendix provides a compilation of peer-reviewed and other publications, proposals to regulatory authorities and key presentations associated with this research study summarised in Figure 1.10 in Chapter One *(Research Introduction and Context)* and referenced in various chapters of the main thesis. The following table is an index to the main study outputs and prior publications that formed the preliminary basis for this research.

	Description † = Lead author | * = Peer-reviewed	# of pages
Prior-Publications Forming Preliminary Basis for Research		
1	Paper†*: Ramnarine, E., Jornitz, M., Long, M., O'Donnell, K., Roenninger, S., Smalley, C., & Vinther, A. (2014). *PDA Technical Report No. 68, Risk-Based Approach for Prevention and Management of Drug Shortages* (Vol. 1, Issue 68)	54
2	Paper†: Ramnarine, E., Roenninger, S., & Vinther, A. (2014). Preventing and Managing Drug Shortages. *PDA Letter*, 4, pp 36–39	4
3	Paper†: Ramnarine, E., & Vinther, A. (2016). PDA Program to Address Post-Approval Hurdles: A Call to Action. *PDA Letter*, *9*, pp 34–35	2
4	Paper†*: Ramnarine, E., Busse, U., et. al. (2017) "PDA PAC iAM^{SM} 2017 Survey on Post-Approval Change: Is the Regulatory Environment Hindering Much-Needed Innovation in the Pharma Industry?" *PDA Journal of Pharmaceutical Science and Technology,* 71 (5), pp 421-427. doi: https://doi.org/10.5731/pdajpst.2017.008219	9
5	Paper†*: Ramnarine, E., Busse, U., et. al. (2017) "PDA Points to Consider: Technical Product Lifecycle Management: Communication and Knowledge Exchange Between Marketing Authorization Holders and Health Authorities" *PDA Journal of Pharmaceutical Science and Technology*, *71* (2), pp 163–169. doi: https://doi.org/10.5731/pdajpst.2016.007492	9
6	Paper†*: Ramnarine, E., Busse, U., et. al. (2017) "PDA Points to Consider: Technical Product Lifecycle Management. Pharmaceutical Quality System Effectiveness for Managing Post-Approval Changes. *PDA Journal of Pharmaceutical Science and Technology*, *71* (3), pp 252–258. doi: https://doi.org/10.5731/pdajpst.2017.007575	9
7	Paper: Vinther, A., Ramnarine, E., & O'Donnell, K. (2017). PQS, An Effective Lever for Managing Post-Approval Changes. *PDA Letter,* 9, pp 42, 44.	2

8	Paper†*: Ramnarine, E., & O'Donnell, K. (2018). Demonstrating Pharmaceutical Quality System Effectiveness and Driving Continual Improvement: Evidence-based Risk Reduction. *PDA Journal of Pharmaceutical Science and Technology*, *72* (3), pp 338–345. Doi: https://doi.org/10.5731/pdajpst.2017.008524	10
Publications During Research Study		
9	Paper†*: Ramnarine, E., Vinther, A., Greene, A., & O'Donnell, K. (2019). "Continual Improvement While Maintaining A State of Control: A Concealed Paradox or a Mutual Interdependence?" *Journal of Validation Technology (JVT)*, *Journal of GXP Compliance (GXP)*, *23*(6).	12
10	Paper†*: Vinther, A., Ramnarine, E. (2019) "Solving the Global Continual Improvement and Innovation Challenge: How an Effective Pharmaceutical Quality System Can Transform Post-Approval Change Management. Industry One-Voice-of-Quality (1VQ) Concept Paper," *PDA Journal of Pharmaceutical Science and Technology,* 73 (5), pp 517-521. doi: https://doi.org/10.5731/pdajpst.2019.010827	7
11	Paper†*: Ramnarine, E., Vinther, A. et.al. (2020) "Industry One-Voice-of-Quality (1VQ) Solutions: Effective Management of Post Approval Changes in the Pharmaceutical Quality System (PQS) – Through Enhanced Science and Risk-Based Approaches.," *PDA Journal of Pharmaceutical Science and Technology,* 74 (4), pp 456-467. doi: https://doi.org/10.5731/pdajpst.2020.011734	14
12	Paper*: Rolke, R., Ramnarine, E. et. al. (2020) "One-Voice-of-Quality (1VQ) Industry Position Paper: Managing Excipient Supplier Name and Address Changes in the Pharmaceutical Quality System," *PDA Journal of Pharmaceutical Science and Technology,* 74 (2), pp 286-288. doi: https://doi.org/10.5731/pdajpst.2019.011239	5
13	Paper†*: Rolke, R., Ramnarine, E. (2020) "One-Voice-of-Quality (1VQ) Industry Position Paper: Changes to Analytical Equipment/Instrumentation that are Deemed Equivalent," *Journal of Validation Technology (JVT), 26* (6).	8
14	Paper*: Lombardi, K., Egal, N. (2020) "One-Voice-of-Quality (1VQ) Industry Position Paper: Shelf-Life Extensions for Pharmaceutical Products," *Journal of Validation Technology (JVT), 26* (6).	11
15	Paper*: Vinther, A., Mohammed, F., Ramnarine, E. (2021) "Industry One-Voice-of-Quality (1VQ) Solutions: Management Review (MR) of Post Approval Changes (PAC) Guide" *PDA Journal of Pharmaceutical Science and Technology.* doi: https://doi.org/10.5731/pdajpst.2021.012627	10
Proposals to Regulatory Authorities		
16	Initial Presentation to PIC/S† – September 2018	15
17	Proposal to FDA – January 2019	27

18	Proposal to PIC/S† – April 2019	1
19	Follow-up Proposal to PIC/S† – June 2020	2
20	Feedback to PIC/S on the Draft PIC/S Recommendation Paper† – November 2020	4
21	Letter from PIC/S QRM Expert Circle Chair Acknowledging Researcher's Contribution – July 2021	2
22	Proposal to WHO – April 2021	7
Key Presentations		
23	Facilitating Continual Improvement, Innovation and Reduced Drug Shortages – Through Enhances Science and Risk-Based Post Approval Change Management – 2020 Annual PDA Conference	22
24	Effective Management of Post-Approval Changes in the Pharmaceutical Quality System – 2020 PDA Europe Conference	20
25	Standard 1VQ Communication Deck – April 2021	18
	Details of *1VQ for PAC* Focus Group Sessions	
26	Details of *1VQ for PAC* Focus Groups 1- 8	48
27	Details of *1VQ for PAC* Focus Group Sessions with Chief Quality Officers and QMS Heads	20
	Drug Shortage Notification Requirements in Legislation and GMPs	
28	Relevant Requirements from the EU Directives, EU GMPs and US FDASIA Laws	2