Managing Risk to the Patient: Recoding Quality Risk Management for the Pharmaceutical and Biopharmaceutical Industries

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Managing risk to the patient:

Recoding Quality Risk Management for the pharmaceutical and biopharmaceutical industries

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A thesis submitted to the Dublin Institute of Technology in fulfillment of the requirements for the award of Doctor of Philosophy (PhD)

Supervisors: Dr. Anne Greene and Dr. Kevin O’Donnell

October 2017
This thesis explores the application of quality risk management (QRM) in pharmaceutical and biopharmaceutical companies and its effectiveness at managing risk to the patient. The objective of the research described in this thesis was to characterize a maturity state of QRM implementation in which the patient is adequately protected from the risks associated with medicinal products of inadequate quality. The research was conducted over three phases: first, to determine whether patients are better protected since the publication of ICH Q9, a commonly employed guidance on the application of QRM; second, to characterize the industry with regard to QRM maturity, including the effectiveness of QRM application, the behaviors, attitudes, and motivations of the people working with and within QRM, and the governance and oversight of QRM efforts; and third, to construct a mature QRM program and associated maturity measurement tool to accelerate improvements in QRM and better protect the patient. The research employed a mixed methods approach, including the research methods of literature review, philosophical dialogues, benchmarking survey, semi-structured interview, and pilot case studies. The research concluded that the patient is no better protected since the inception of QRM and the level of QRM maturity throughout the pharmaceutical and biopharmaceutical industries remains rather low. However, the research also indicated that progression towards the more mature QRM model proposed in thesis may help firms perform QRM in a more effective manner, resulting in improved management of risk to the patient.
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 Dublin Institute of Technology 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 report conforms to the principles and requirements of the DIT’s guidelines for ethics in research.

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Signature

Date 31 Oct 2017
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And to the most important person of all—my husband, my teammate, my love, and my life. You support me in all things. I don’t want to spend a moment of life without you. I love you.
**List of Abbreviations**

**API** = Active Pharmaceutical Ingredient

**BLA** = Biological License Application

**CA** = Critical Aspect

**CADE** = Critical Aspect Design Element

**CAPA** = Corrective and Preventive Action

**CFR** = Code of Federal Regulation (US)

**CMO** = Contract Manufacturing Organization

**COGS** = Cost of Goods Sold

**COSO** = Committee of Sponsoring Organizations of the Treadway Commission

**CPP** = Critical Process Parameter

**CQA** = Critical Quality Attribute

**CRO** = Contract Research Organization

**DQ** = Design Qualification

**EMA** = European Medicines Agency

**EU** = European Union

**FAQ** = Frequently asked question

**FDA** = Food and Drug Administration (United States of America)
**FMEA** = Failure Modes and Effects Analysis

**FTE** = Full time equivalent

**GMP** = Good Manufacturing Practice. Also cGMP, “current” Good Manufacturing Practice

**HACCP** = Hazard Analysis and Critical Control Points

**HPRA** = Health Products Regulatory Authority (formerly Irish Medicines Board; Ireland)

**ICH** = International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (formerly International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use)

**IQ** = Installation Qualification

**ISPE** = International Society for Pharmaceutical Engineers

**IVT** = Institute of Validation Technology

**KPI** = Key Performance Indicator

**MAH** = Marketing Authorization Holder

**MHRA** = Medicines and Health Products Regulatory Agency (United Kingdom)

**NASA** = National Aeronautics and Space Administration

**NDA** = New Drug Application

**NRC** = Nuclear Regulatory Commission

**OQ** = Operational Qualification
**PDA** = Parenteral Drug Association  

**PMA** = Premarket Approval  

**PRST** = Pharmaceutical Regulatory Science Team (DIT)  

**PQ** = Performance Qualification  

**QbD** = Quality by Design  

**QRM** = Quality Risk Management  

**QTPP** = Quality Target Product Profile  

**REMS** = Risk Evaluation and Mitigation Strategies  

**RIMS** = The Risk Management Society  

**ROI** = Return on Investment  

**RMP** = Risk Management Plan  

**RRF** = Risk Ranking and Filtering  

**SOP** = Standard Operating Procedure  

**US** = United States of America  

**WHO** = World Health Organization
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1 Chapter One: Introduction

This thesis outlines the objectives and progress of the research study into quality risk management maturity within the pharmaceutical and biopharmaceutical industries, based upon the International Council on Harmonisation (ICH) Guidelines Q8 Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System. The research study commenced in July 2014 for the explicit purpose of inquiring as to the value that Quality Risk Management (QRM) brings to the patient, and how best to define, measure, and accelerate risk maturity in the pharmaceutical and biopharmaceutical industries. For the purposes of this thesis, the term “risk maturity” is used interchangeably with “quality risk management maturity” and is defined as the level of effectiveness of a QRM program to bring value to the patient.

This thesis consists of four sections and twelve chapters in total, as shown in Table 1-1. This chapter serves as a general introduction to the industrial and regulatory climate in which the research is being conducted, as well as the focus of the research and problem it addresses.

Section One, inclusive of Chapters Two and Three, describes the foundations of the research.

Chapter Two provides an overview of the literature review conducted, including a critical analysis of the ICH guidelines that serve as a primary input into the research.
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Chapter Three explores the ontological underpinning of the research, the research question, the methods and methodology, and reviews the progression of the research throughout its tenure.

Section Two includes Chapters Four, Five, and Six, targeted at characterizing the current state of quality risk management in the pharmaceutical and biopharmaceutical industries.

Chapter Four explores the extent to which the patient has realized the benefits of QRM through improved quality of medicines.

Chapter Five details the current state of industry with regard to QRM practices and perceptions.
Chapter Six explores the application of risk management in other industries, including medical devices, aerospace, and nuclear power, and explains key learnings that were applied in later stages of the research.

Section Three of this thesis, composed of Chapters Seven, Eight, Nine, and Ten, defines the ideal state with regard to QRM and provides a comprehensive tool kit to assist industry with progressing towards this ideal state.

Chapter Seven focuses on the people working within the ideal QRM program, including the knowledge and culture necessary to enable risk maturity.

Chapter Eight re-envisions the QRM process to strengthen the link between QRM activities and patient protection.

Chapter Nine outlines the purpose of governance within a mature QRM program and defines critical elements and structure necessary to achieve excellence.

Chapter Ten completes Section Three by describing a measurement tool to gauge the level of risk maturity at a given company and facilitate progression towards the ideal state.

Section Four, the final section of the thesis, summarizes the research effort and suggests areas for continued evolution of QRM.

Chapter Eleven provides suggested focus areas for future research into QRM.
Chapter Twelve concludes the research effort and offers recommendations to industry and regulators to better manage risk to patients.

The research study described in this thesis focuses on quality risk management (QRM), a relatively recent concept that involves the application of risk management principles and practices to the control and enhancement of drug product quality. The goals of QRM are myriad, but in the researcher’s view may be summarized as follows:

*Quality risk management aims to protect the patient through the understanding and management of product quality risks.*

The sections that follow will briefly introduce the climate in which pharmaceutical and biopharmaceutical companies operate, the concepts of risk and risk management, and the types of risks the research explores. Finally, the problem the research seeks to address is presented.

### 1.1 Research context

Looking over the roughly 6,000 years of societal history, several scientific advances stand out as truly transformational—advances that changed the world. The most revolutionary of these was the dawn of modern medicine. Borne of necessity (and some creativity), modern medicine has enabled a consistent, scientific approach to the diagnosis and treatment of human disease, increasing the human lifespan and enhancing the quality of the lives lived within it. The lion’s share of the credit for these achievements goes to the advent of medicinal products. These products tackle the
causes of human disease, alleviate debilitating symptoms, and empower our species to focus beyond mere survival towards other endeavors; as a result, medicinal products have enabled human progress. The pharmaceutical and biopharmaceutical industries (collectively termed “industry” throughout this thesis) are two of the bodies that discover, develop, and manufacture these products for human use. The contribution of these industries to human health is immeasurable; these industries are the engines behind modern medicine.

Medicinal products are defined as “any substance or combination of substances presenting as having properties for treating or preventing disease in human beings.” (1)

There are generally considered to be two types of medicinal products: pharmaceuticals and biopharmaceuticals.¹ Both pharmaceutical and biopharmaceutical products are intended to affect the structure or function of human physiology in order to diagnose, cure, mitigate, treat, or prevent disease. (2) Pharmaceutical and biopharmaceutical products differ primarily in their manufacturing process, either through traditional chemical isolation or synthesis or through a biological process involving natural (biological) sources. The term “drug” is synonymous with “medicinal product” and is used to describe both pharmaceuticals and biopharmaceuticals.

Over time, the extent to which the world relies on drugs to protect and advance human health has steadily increased. Worldwide revenue of the global pharmaceutical market grew from US$390.2 billion in 2001 to $1.1 trillion in 2014, with global drug spending

¹ Technology is increasingly blurring the lines between the typology of medicinal products. For example, many newer products incorporate both a medical device and a medicinal product, or a biological product with a pharmaceutical product, creating a new class called “combination products.” So as to not unnecessarily complicate the concepts, this research paper will focus on pharmaceuticals and biopharmaceuticals, irrespective of any associated sub-classifications.
expected to reach $1.4 trillion by 2020. (3) Biopharmaceuticals are expected to capture a larger proportion of spending in the near term, with expected revenues of $445 billion by 2019. (4) These monetary figures are rough (and perhaps imprecise) surrogates for the true measure of the breadth and strength of the drug industry—the number of patients served. Regardless of debates around drug pricing, costs associated with production and distribution, and access strategies in developed and emerging markets, the number of patients with access to medicines continues to increase.

The success associated with treatment rates is undermined, however, by several very real and very grave facts. Despite consistent progress in this area, not all patients who need drugs have access to them. Of those patients who do, this access can be threatened by myriad issues, including quality problems. Consider, for example, Roche’s antiretroviral medicine Viracept (nelfinavir). This product treats HIV-infected patients of all ages, and was hailed as a medical breakthrough throughout the world for its effectiveness in alleviating the symptoms and disease progression of HIV. The relatively low cost of the drug allowed for a relatively broad level of global access to this product, particularly in historically underserved regions such as Africa— that is, until a manufacturing quality problem resulted in a temporary but significant market withdrawal in 2007. A simple manufacturing issue (improper cleaning of a tank) had resulted in the creation of a genotoxic impurity known as ethyl mesylate. A large-scale recall of the drug was initiated in response, leading to a lack of treatment for large patient populations with deadly consequences. (5) (6)

Another example of quality problems hindering access to life-saving medicines occurred in 2009, due to a viral contamination event at the Genzyme plant that manufactured the biopharmaceutical drugs Cerezyme and Fabrazyme. Cerezyme and
Fabrazyme treat rare genetic diseases known as Gaucher’s and Fabry’s, respectively. Both Gaucher’s and Fabry’s disease are lysosomal storage disorders—diseases in which the body lacks certain enzymes necessary to break down fatty acids, resulting in the buildup of these chemicals in the body. (7) (8) Left untreated, most patients succumb to their disease. (9) (10) When a viral contamination event at Genzyme left the company unable to continue to supply product to market, many patients had no choice but to reduce their dosing schemes or forgo treatment altogether, ultimately leading to several deaths. (11) (12) The impact of these drug shortages echo to the present day—while the Fabrazyme shortage was resolved in July 2016, Cerezyme remains on critical medicines shortage lists—a full seven years after the contamination event. (13)

These incidents, among others, eroded the trust between industry and the public; after all, these events were ultimately predictable and avoidable. One technique with a proven history of success has been used in many industries (such as finance, nuclear energy, and aerospace) to predict and avoid such crises. This technique, risk management, is at the core of this research effort.

1.2 Overview of risk management principles and practices

“Risk” has become a ubiquitous term in contemporary society, but is used in such a wide variety of contexts that its meaning has been blurred. The International Organization for Standardization (ISO) defines risk as “the effect of uncertainty on objectives.” (14) Indeed, the world is riddled with uncertainty—a necessary byproduct of our inability to foretell the future. In the event the future could be precisely predicted, it could be controlled, rendering all types of endeavors successful. Unfortunately, this
is not the world we live in, nor the world in which businesses operate. As such, “all activities of an organization involve risk.” (15)

The mere existence of risk does not imply a foregone conclusion of failure, of course; risk can be both defined and calculated, allowing the exercise of some influence in the form of knowledge. The magnitude of risk is calculated as the combination of the probability of occurrence of harm and the severity of that harm, exhibited in a simple equation: (16)

\[ \text{Likelihood} \times \text{Severity} = \text{Risk} \]

This calculation captures the main concerns associated with risk—the chances that some undesirable event will occur, and how bad it might be if it does. The level of concern rises as egregious outcomes become increasingly likely, and subsides when consequences are less severe or rarer. In this way, the concept and calculation of risk reflects the general amount of apprehension with which we approach various activities.

It follows that the management of risks is necessary to increase the probability that an identified goal will be achieved. For example, a thrill-seeking sky diver does not blindly launch him or herself out of an airplane; rather, specific safety controls are employed to ensure the jump will be successful. In the context of business, risk management is defined both as “coordinated activities to direct and control an organization with regard to risk” and the “systematic application of management

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2 Because the term “risk” is both a concept and an equation, the term “hazard” has been introduced to make a more clear distinction. Hazards are defined as “potential sources of harm,” (16) and serve to replace the concept (noun) form of the term “risk.” However, because this distinction may confuse those who do not specialize in risk management, in most cases throughout this report the terms “risk” and “hazard” are used interchangeably.
policies, procedures and practices to the activities of communicating, consulting, establishing the context, and identifying, analyzing, evaluating, treating, monitoring and reviewing risk.” (14) Using the latter definition, risk management is universally acknowledged as a process consisting of the identification of risks, the analysis of risks to determine their criticality (using, for example, the risk equation listed above), and the disposition of risks based on organizational objectives. The risk management process is then repeated as the internal or external business climate evolves. (15)

The goals of risk management vary based upon the intent of application. For example, risk management may be employed to:

- increase the likelihood of achieving objectives
- encourage proactive management
- increase awareness of the need to identify and treat risk throughout the organization
- improve the identification of opportunities and threats
- comply with relevant legal and regulatory requirements and international norms
- improve mandatory and voluntary reporting
- improve governance
- improve stakeholder confidence and trust
- establish a reliable basis for decision making and planning
- improve controls
- effectively allocate and use resources for risk treatment
- improve operational effectiveness and efficiency;
- enhance health and safety performance, as well as environmental protection
- improve loss prevention and incident management
- minimize losses
- improve organizational learning, and
- improve organizational resilience (15)
Regardless of the individual goal for which risk management is invoked, it is always used to help ensure business objectives are met. With regard to medicinal products, therefore, risk management assures the safety of the patient and the effectiveness of the drug. The application of risk management is vital to ensure the primary business objective of these industries is met: to serve the patient.

1.3 The general focus of the research

Within the realm of medicinal products, one can identify two general categories of risk to the patient: intrinsic risk and extrinsic risk. Table 1-2 delineates the various characteristics of, and differences between, these two categories of risk.³

Intrinsic risks are those inherent to a given drug, given the nature of certain biochemical reactions within the body when exposed to a drug or its constituent parts. Intrinsic risks generally surface during research and development and in the clinic, and are weighed against the overall medical benefits of the product when determining whether the drug is suitable for commercial sale. For example, while the risk of suicidal thoughts or feelings might be considered acceptable in the context of an antidepressant medication where such underlying urges may already be present, that same risk would be unacceptable if it were to accompany a mild pain-reliever such as ibuprofen. The acceptability of intrinsic risks is therefore relative, based on the therapeutic benefits a drug delivers.

³ While some sources allude to these different types of risks, few make a clear distinction between intrinsic and extrinsic risk (excepting the FDA Risk Management Task Force (40)). As such, and because this distinction is crucial to understand the scope and focus of the research, most of the ideas in this section are the researcher’s alone.
Table 1-2: Intrinsic vs. extrinsic risk

<table>
<thead>
<tr>
<th>Types</th>
<th>Intrinsic risks</th>
<th>Extrinsic risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The medicinal product itself</td>
<td>External events or circumstances</td>
</tr>
<tr>
<td>Types</td>
<td>Adverse reactions • Risks communicated via warnings / precautions • Contraindications</td>
<td>Dosing or medication errors • Counterfeiting or tampering • Shortages • Quality risks (the focus of this research)</td>
</tr>
<tr>
<td>Communicated to</td>
<td>Labeling • Medication guides • Specific risk management plans</td>
<td>Special notices (reactively identified events) • Almost never (proactively identified circumstances)</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identified through</td>
<td>Clinical studies • Post-market pharmacovigilance</td>
<td>Complaints • Deviations • Proactive quality risk management</td>
</tr>
<tr>
<td>Managed through</td>
<td>Market authorization holder (MAH) to patient communication and risk management plans</td>
<td>Corrective and preventive action (CAPA) • Risk reduction/mitigation</td>
</tr>
<tr>
<td>Potential</td>
<td>Range from negligible to life-threatening</td>
<td>Range from negligible to life-threatening</td>
</tr>
<tr>
<td>consequences to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>patient</td>
<td></td>
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</table>

Generally, intrinsic risks are communicated to patients and their healthcare providers through product labeling. Labeling allows for the sharing of intrinsic risk information so that patients, in consultation with their medical teams, can make informed decisions regarding the course of their care. While requirements for drug product labeling vary by region, in most instances the communication of intrinsic risks can be subdivided into a number of categories, including adverse reactions, warnings and precautions, and contraindications. Adverse reactions (known in some regions as side effects or
undesirable effects) are conditions that the patient might reasonably expect to occur during use of the medicinal product that are undesirable in nature. (17) Adverse reactions are numerous and variable, and may include (but are certainly not limited to) dry mouth, drowsiness, stomach pain, nausea, vomiting, or diarrhea. Side effects are often discovered over the course of clinical trials, and may be further refined through data from adverse event reporting, complaints, and pharmacovigilance activities that occur in the commercial phase of the product lifecycle.

Warnings and precautions are extensions of adverse reactions that might threaten the patient’s health and well-being, either because the adverse reaction is severe enough to impact decisions regarding a patient’s care or because the adverse reaction might require more specific precautions to be communicated to the patient. (18) For example, the common analgesic and fever reducer paracetamol (called acetaminophen in the US) comes with a warning regarding liver failure in doses in excess of recommendations. (19) (20) Intrinsic risks grouped within warnings and precautions are often discovered during drug development but may also be included to highlight logical consequences of known side effects (as is the case, for example, when drugs that cite drowsiness as an adverse reaction also include a precaution against driving and operating heavy machinery). Warnings and precautions, therefore, are derived from risk assessments in which the gravity of the risk (likelihood of harm, severity of the harm, or a combination thereof) or consequences of drug administration might pose a threat to the patient in an unintended way.

Contraindications are an additional class of intrinsic risk in which a causal relationship between the drug and some other physiological condition (a disease condition or cohort of the patient population) exists and may result in an adverse reaction. (18) For

26
example, certain drugs may be contraindicated for use in children, pregnant or lactating women, or the elderly, while others may be ill-advised for administration when the patient is immunocompromised due to a co-existing condition. In addition, certain drugs may interact with other drugs, resulting in serious consequences that jeopardize the patient’s overall health, as is the case when two classes of antidepressant drugs (monoamine oxidase inhibitors, or MAOIs, and selective serotonin reuptake inhibitors, or SSRIs) are used simultaneously. (21)

Regulatory authorities around the world base product approval decisions on a variety of factors, the most important of which is the benefit-risk profile.4 This evaluation weighs the intrinsic risks of the product (such as the nature of adverse reactions that may occur, the relative severity of the reactions, and their estimated or confirmed rate of occurrence in the target patient population) against the medical benefits of the product. In most cases, the benefits of the product must clearly outweigh the risks in order to be considered appropriate for commercial use; panels of experts are often used to guide the final decision, though quantitative risk assessment models may be employed to calibrate the scientific judgment of decision-makers. (22) In some cases, however, the data may reveal that the benefits outweigh the risks only in certain circumstances, or certain risks are severe enough to warrant additional management to ensure the benefit-risk profile remains favorable. In these instances, a regulatory authority may call for the proposal and enactment of a risk management plan (RMP) to manage these risks in a commercial setting.

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4 In some regions, such as the US, and with some products, such as medical devices, the term “risk-benefit” is used to denote this concept.
Risk management plans (referred to as Risk Evaluation and Mitigation Strategies, or REMS, in the US), are plans to manage intrinsic risk through the application of targeted controls. The nature of the controls varies based on the risk, and are intended to assure that the medical benefits of the drug product continue to outweigh the risks. (23) For example, the medication isotretinoin (originally marketed under the brand name Accutane) offers significant relief to patients with severe acne, a painful condition that can negatively impact patients’ self-confidence. Isotretinoin is incredibly effective in the treatment of acne, in most cases eliminating the condition altogether; however, it can also cause severe birth defects. (24) Despite the fact that the drug’s labeling documents a contraindication for pregnant women, a risk management plan was deemed necessary in order to ensure that women would not become pregnant while using the product. The REMS for isotretinoin, called iPledge, includes a medication guide, a certification program for prescribing physicians and dispensing pharmacies, and mandatory enrollment of patients in the iPledge program. Risk controls associated with the iPledge program include limited prescribing allowances (no more than 30 days of medication with no refills at any time), contraception counseling between the healthcare provider and patient, two pregnancy tests performed prior to drug administration with monthly follow up tests thereafter, certification from the patient that she will use two forms of contraception throughout the treatment period, and other similar controls. (25) These additional risk controls are intended to ensure that the benefits of isotretinoin (the treatment and potential elimination of severe acne) outweigh the risks (severe birth defects) by preventing fetal exposure to the drug.

Regulators and industry acknowledge that the data obtained during drug development and clinical testing may not be sufficient to reveal all intrinsic risks. As a result,
ongoing pharmacovigilance is required. Pharmacovigilance is “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.” (26) Conducted in a post-market environment, these programs enable the identification of signals that might indicate a new intrinsic risk, or provide additional data regarding the frequency and severity of known risks that can further inform the benefit-risk balance. (27) New information gleaned from pharmacovigilance may result in the discontinuation of a product. For example, the popular weight loss drug fenfluramine was discontinued in 1997 after pharmacovigilance activities revealed a correlation with heart valve disease and pulmonary hypertension, conditions not previously identified in clinical trials. (28)

Historically, pharmacological research and drug approval regulation have focused primarily on these intrinsic risks; as such, intrinsic risks garnered the most industry and regulatory scrutiny. Patients benefit from the broad communication of intrinsic risks through mechanisms that include product labeling, as described above, as well as tightly regulated risk management in the form of initial product approval decisions, risk management plans that may be required during commercialization, and ongoing pharmacovigilance. However, intrinsic risks are only a portion of the total risk a patient may be exposed to during their use of a medicinal product. The other category of risks, extrinsic risks, may have similarly grave consequences, yet have been comparatively neglected until recent times.

Extrinsic risk can be defined as unintended risks to the patient arising from events or circumstances unrelated to the drug product itself; for example, dosing errors, counterfeiting or tampering, drug shortages, or risks introduced during manufacturing,
packaging, labeling, distribution, or storage. A critical subset of these are quality risks—risks to patients that are associated with the quality of the medicinal product.

Quality risks are a nefarious bunch. Because quality problems often manifest as failures to meet specifications, and because drug specifications address chemical and biochemical attributes of the product, quality problems are often invisible to the patient. Quality problems can vary by manufacturer and batch—as such, the same drug might expose patients to different quality risks, depending on the brand or product lot number. Patients are rarely informed of the potential quality risks associated with a given product, limiting their ability to make informed choices about their healthcare by restricting their access to critical information. Finally, quality risks may greatly affect the benefit-risk balance of product, since products are approved for sale based on a favorable benefit-risk ratio, and quality risks introduce new considerations in that equation.

Patients and healthcare providers have an inherent assumption that a product’s intrinsic risk has been accepted through regulatory approval, and that the drug they administer or receive is both safe and effective. Regulators and industry acknowledge, of course, that deviations from cGMP and product-specific quality attributes could threaten the critical link between an individual dose of a medicinal product and its marketing authorization, thereby rendering the drug “adulterated.” In other words, any quality risk imposed in addition to the drug’s intrinsic risk upsets the benefit-risk balance, and should therefore be identified and controlled. Despite the criticality of quality risks, they were overshadowed by the concern with intrinsic risks until recent times.
1.4 Problem this research addresses

When patients take a medicine, they exercise their trust in the pharmaceutical industry. They trust that the product is as it is labeled, and that no external circumstance might put them at risk beyond that disclosed in the labeling. They trust that drug manufacturers have produced the product in safe and consistent way, and that their health and safety is protected. The market does not distinguish between high or low-quality drugs, because acceptable quality is presumed to be present. (29)

As recent events attest—this assumption is far from the truth. While the sources of quality problems, consequences of poor quality drug products, and the resultant patient impact have been well documented, a rigorous inquiry into a methodological approach to the resolution of these issues is notably absent. This research effort seeks to fill this gap by defining the effective use of QRM, a key solution for the “quality problem.”
Section One: A Brief History of Risk and Research
“Risk is like fire: If controlled it will help you; if uncontrolled it will rise up and destroy you.”

- Theodore Roosevelt

"The easy way out usually leads back in."

- Peter Senge
The research commenced with a review of the extant literature. There is a wealth of texts on the topic of QRM in the pharmaceutical and biopharmaceutical industries, from sources spanning regulations, regulatory guidance documents, books, industry whitepapers, peer-reviewed articles, presentations from regulators and industry practitioners, and commentary and opinion pieces. Because the literature is rich with different perspectives, many of which illustrate the evolving understanding of QRM that is so pivotal to the research, the researcher has included, where applicable, a thoughtful appraisal of various conceptual breakthroughs, thought leadership, and shortcomings. The literature serves as a consistent element of the research design and is drawn upon heavily in later chapters as well.

This chapter focuses on the literature review performed to orient the researcher in the topic of QRM within industry. The chapter begins with a brief (and therefore self-consciously incomplete) history of risk management in the pharmaceutical and biopharmaceutical industries. The applicable ICH guidelines that serve as the foundation of the research effort are then reviewed, followed by QRM-related books and technical reports issued by industry thought leaders. The literature review as documented in this chapter proceeds chronologically by source, rather than by theme, in order to demonstrate the evolution of thinking on QRM related topics over time.

Additional chapters of the final thesis will include topic-specific literature reviews as applicable to the phases of the research:
• Chapters Four and Five describe the conduct and outcomes of the Phase 1 and 2 research, focused on characterization the current state of industry with regard to QRM implementation and benefit realization. The literature discussed in these chapters support this baseline characterization, including potential contributing factors that may have influenced the current state.

• Chapter Six explores the application of risk management in industries with longer and more mature histories of its use. The literature discussed in Chapter Six will serve as the primary source for this external benchmarking.

• Chapters Seven, Eight, and Nine describe the conduct and outcomes of the Phase 3 research, focused on defining a mature state of QRM application to enable industry to perform QRM activities more effectively. The literature discussed in these chapters will help define the ideal state from a variety of perspectives, including regulation, industry, and academia.

Figure 2-A maps the various topics to be explored as part of the literature review with the applicable chapters or section in which they are discussed.

![Figure 2-A: Literature map](image-url)
Rather than proceeding chronologically by source, as in this chapter, the supplemental literature reviews will discuss the literature by theme as the full breadth of ideas in the research effort are introduced.

2.1 The emergence of quality risk management as a concept and a discipline for medicinal products

2.1.1 Early pharmaceutical risk management

Risk management has been a foundational element of the regulation of healthcare products since the inception of related regulatory bodies; indeed, one could argue that the primary reason such regulatory bodies exist is to protect the public from health and safety risks associated with medicinal product use.

Some sources date early formularies, known as pharmacopeias, back to first century AD Greek texts (such as Pliny’s catalogue of medicinal herbs in *Naturalis Historae*). (30) The earliest known regulation for such pharmacopeia was the Salerno Medical Edict issued by Frederick II of Sicily in 1240, which required apothecaries to prepare their medicinal remedies in the same way. (31) Such laws, which became increasingly pervasive throughout the European continent during medieval times, recognized that consistency across drug formulations was necessary in order to assure the intended effects of the product, thereby minimizing risk to the patient.

The late 19th century saw additional drug legislation come into effect. In the US, the first such legislation occurred following the Mexican-American war of 1846 – 1848, during which American soldiers were administered various drugs for a host of maladies (including malaria, yellow fever, and cholera). Many of these drugs were imported,
and some proved to lack the safety and efficacy needed to fully protect the troops. The large number of deaths that occurred in that period can be attributed not only to the typical slaughter seen in wartime, but also to these faulty drugs. The US Import Drug Act of 1848 was sanctioned to ensure that any such imported drug was subject to purity and quality testing prior to passing through the border. (32) The Import Drug Act established a theme for drug regulation the world over—advances in pharmaceutical regulation general occur as a consequence of *tragedy in the public eye*, seeking to manage risk to patient safety and health *reactively*.

In the US, which represents the world’s largest population of drug consumers, the growth in both scope and statute of the FDA was borne of several highly publicized tragedies. Figure 2-B illustrates this trend for selected early milestones in American drug law. (31) (32) (33) (34)

This pattern of *reactivity*, where healthcare disaster is antecedent to advances in regulatory science, continues to the present day. For example, the heparin scandal of 2008 led to many dozens of deaths, followed by a surge in attention to the management of Active Pharmaceutical Ingredients (APIs) and control over the increasingly complex supply chain. (35) (36) While this reactive process serves to prevent future injury and death, one is left with a tinge of regret at the prospect that such tragedies could have been anticipated and avoided with the application of right tools and the right conviction.
2.1.2 The precautionary principle

The precautionary principle represents one of the first proactive risk management mindsets to reach the public sphere. Originally discussed in the context of environmental law making, the principle asserts that when faced with uncertainty regarding a given risk, particularly when the consequences of the risk may have serious and lasting effects, an abundance of caution must be used to provide the desired level of protection to society. 5 (37) (38) The principle serves as a decision-making guideline for regulators, to be invoked in circumstances where scientific evidence regarding a certain risk is lacking. In these cases, a failure to actively avoid the risk could lead to an incredible amount of damage, both of person and of cost; therefore, the only

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5 While the precautionary principle was first formally implemented in 1974 in a German law on clear air (39), the researcher suggests that the main tenets of the principle have been engrained in human nature throughout our existence. The inherent risk- (and likewise uncertainty-) aversion of the species has enabled survival over millennia, as otherwise our curiosity would most certainly have gotten the best of us.
appropriate response is to implement the appropriate measures (such as banning a given substance) to protect the public while simultaneously seeking to increase understanding of the risks. (37) (38)

As a decision aid, the precautionary principle can be viewed as a rudimentary risk management process, as illustrated in Figure 2-C. (37) (38) (39)

The proactive nature of the precautionary principle stems from the early identification of sources of uncertainty, combined with the concerted effort to avoid the associated risk until the uncertainty can be reduced or eliminated. In this way, the concept of risk is linked with scientific knowledge, such that appropriate risk management can only be effectively applied where there is sufficient understanding upon which sound conclusions can be drawn. The precautionary principle and the effects of uncertainty will be explored further in Chapter Six.
Potential risk

Is the risk highly uncertain?

Evaluate the potential consequences of the risk to determine harmful effects

Are the consequences very severe?

Evaluate costs and benefits of inaction

Will society be adequately protected if we do nothing?

Take action (e.g., withdraw or ban substance)

Conduct risk assessment; make decisions based on benefit-risk profile

Conduct scientific studies to improve understanding of the risk and its probability of harm

YES

NO

YES

NO

Figure 2-C: Decision tree illustrating the application of the precautionary principle, as proposed by the researcher
2.1.3 Modern inquiries into the role of risk management in pharmaceutical regulation

Modern exploration of risk management for pharmaceuticals arose with a 1999 report to the FDA commissioner from the Task Force on Risk Management\(^6\). This task force, established by then-commissioner Dr. Jane Henney, was tasked with determining the technical soundness, consistency, and validity of risk management activities ongoing within FDA at the time, and the construction of recommendations to improve the effectiveness and efficiency of these activities. The final report from the Task Force, entitled *Managing the Risks from Medical Product Use: Creating a Risk Management Framework*, focused on the premarket risk assessments\(^7\) performed in support of New Drug Applications (NDAs) for pharmaceuticals, Biological License Applications (BLAs) for biopharmaceuticals and biologics, and Premarket Approvals (PMAs) for medical devices, as well as post-market surveillance activities. (40) The report did not explore quality-related risk management, explaining that “injury from product defects is unusual in the United States because of the great attention paid to product quality control and quality assurance during manufacturing.” (40) Despite this claim, the report goes on to cite several case studies of injury and death that, through a contemporary understanding of product quality, could be traced to a lack of QRM.

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\(^6\) Some earlier regulation and guidelines had sought to apply risk management processes from engineering trades to medical devices, particularly in concert with design control. These began in 1993 in the EU with the issuance of 93/42/EEC, commonly known as the Medical Device Directive, followed in the US with the issuance of “Design Control Guidance for Medical Device Manufacturers” in 1997. Internationally, ISO 14971 from 2000 and ISO 13485 in 2003 strengthened the link between risk management and product development. The application of risk management in medical devices is discussed further in Chapter Six.

\(^7\) Premarket risk assessments are primarily comprised of the benefit-risk assessments described in Chapter One.
One example describes a spate of product mix-ups that led to the administration of the wrong drug in a hospital setting, leading to three injuries and one death. The distributor, Burroughs Wellcome, packaged the implicated product in a similar way to other products—including a foil overlay with a transparent window through which the original product labeling could be viewed. The design of this foil overlay allowed for movement of the product within, allowing for the product label to slip below the viewing window, rendering the contents of the package difficult to determine. Sadly, this was the root cause of the injuries and death, as the incorrect product was administered to unwitting patients. (40) The report did not acknowledge that the application of QRM to the foil overlay design might have allowed for the anticipation and avoidance of such use errors.

Despite the (perhaps myopic) scope of the report, several recommendations were proposed to improve risk communication and early intervention in the event a potential risk is realized. (40) These recommendations ultimately contributed to the implementation of several successful programs at FDA\(^8\), serving their goal to leverage improved data collection and risk management to better protect public health.

While the 1999 report from the FDA Task Force on Risk Management marked one of the first contemporary, explicit inquiries into the existence and effectiveness of risk management and risk-based decision making from regulatory authorities, the topic of quality risk management was not addressed.

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\(^8\) Improved data collection and risk communication programs include the formalization of REMS (Risk Evaluation and Mitigation Strategy), a post-approval program intended to manage serious patient risks associated with new medicinal products as described in Chapter One, and Sentinel, an improved adverse event reporting system.
A fully-formed concept for proactive risk management, inclusive of the management of both intrinsic and extrinsic risks, emerged in August 2002 with the announcement of a new FDA initiative, entitled *Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach*. The objectives of this initiative were as follows:

- “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 quality systems approaches into the Agency’s business processes and regulatory policies concerning review and inspection activities” (41)

The final report on the initiative, issued in September 2004, laid out the framework through which FDA intended to meet or encourage these objectives. While only one of the goals explicitly listed risk management as a focus area, a careful reading of the final report reveals that risk principles scaffold the plan.

The report foretold the adoption of a quality systems model for quality management and regulation, to be applied by both industry and FDA alike. While the quality systems concept had been implemented for some time within medical device regulation (for example, within ISO 13485, *Medical devices – quality management systems –*
requirements for regulatory purposes, and 21CFR820, *Quality System Regulation*), the idea of such a system within pharmaceutical and biopharmaceutical circles was novel.

Several advances in regulatory science had been made under the umbrella of the 21st Century initiative, combining knowledge gained through state-of-the art science and technology with a risk-based orientation. These include, for example:

- Creation of a risk-based model for inspectional oversight\(^9\)
- Issuance of a new guidance on aseptic processing, entitled *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*, to emphasize the need to proactively prevent contamination during sterile product manufacturing and to further encourage the adoption of risk management principles in the assurance of sterility (41)

The 21st Century initiative marked a paradigm shift in pharmaceutical regulation; a transition away from *rule-based* compliance (in which the emphasis was on following statute, often at the expense of developing a deep understanding of products, processes, and associated risks) towards a *risk-based* view of quality and compliance. In the context of this research, perhaps the most interesting emphasis throughout the 21st Century initiative final report is the repeated use of the phrase *efficient risk management*. The implications here are, of course, that risk management, if not

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\(^9\) The FDA employs a risk-based model to prioritize sites for inspection based on the type of products made, the target patient population, historical compliance history, and trends associated with recent quality and cGMP-related events. The model is codified in a September 2004 document entitled *Risk-based Method for Prioritizing cGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model*. The PIC/S community published their model in January 2012, entitled *A Recommended Model for Risk-based Inspection Planning in the GMP Environment*. While some variations in the risk method exist, the two models are more similar than they are different, illustrating how regulatory authorities often have convergent ideas of risk factors, regardless of their origin.
performed properly, can be inefficient. This is quite a curious prospect, given that one of the reasons a risk-based framework would be employed for a given problem is to ensure that resources are efficiently allocated towards the things that matter most. The concept that risk management should be performed in an efficient and effective manner to yield an efficient and effective outcome for the patient, serves as a cornerstone of this research study.

2.2 International Council on Harmonization (ICH) Guidelines

2.2.1 Introduction to ICH

The ICH is a cooperative effort comprised of regulatory authorities around the world, working together to create a single set of harmonized guidelines through which the pharmaceutical and biopharmaceutical industries can operate. ICH was born of the need to speed much-needed therapies to patients without the burden of excessively divergent scientific and technical legislation around the world. (42)

The ICH espouses its mission as “…to make recommendations towards achieving greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines.” 10 (43) The mechanism through which ICH accomplishes this mission is the creation of harmonized guidelines, aimed at providing industry with a clear

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10 Note, though the ICH undertook some organizational changes and an associated rebranding in October 2015, this mission statement appears to date to 2000, a time when ICH was focused primarily on product registration at the expense of later phases of product lifecycle management. It is now clear that the scope of ICH has evolved beyond the early phases of research and development. Perhaps a new mission statement covering the current scope of the ICH will be issued in the future.
framework that, if followed, addresses many of the expectations of international regulators. ICH guidelines are divided into four main categories, as indicated in Table 2-1.

This research study focuses on the more recent ICH Quality guidelines published between June 2005 and May 2012 (ICH Q8(R2), Q9, Q10, and Q11), including a prospective guideline (ICH Q12) that has not yet been published. Collectively, these guidelines outline the framework within which QRM operates; therefore an introduction to the general concepts is in order.

Table 2-1: ICH guideline categories

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Guideline Type</th>
<th>Examples and Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q</td>
<td>Quality</td>
<td>“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.” (44)</td>
</tr>
<tr>
<td>E</td>
<td>Efficacy</td>
<td>“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.” (44)</td>
</tr>
<tr>
<td>S</td>
<td>Safety</td>
<td>“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.” (44)</td>
</tr>
<tr>
<td>M</td>
<td>Multi-disciplinary</td>
<td>“… 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).” (44)</td>
</tr>
</tbody>
</table>
2.2.2 Quality Risk Management: ICH Q9

ICH Q9, *Quality Risk Management*, represents the first internationally recognized guideline specifically addressing QRM for the pharmaceutical and biopharmaceutical industries. Published in June 2005, the guideline offers an overview of general quality risk management principles, an example of a risk management lifecycle, discussion around the activities that occur in each lifecycle phase, and a listing of risk tools and quality system areas to which QRM can be applied. This section discusses ICH Q9 in detail, including generally accepted interpretations of the intent and application of the guideline.

In the introduction to the guideline, ICH acknowledges that risk management has been used with much success in other industries, as well as to measure and monitor the intrinsic risk of pharmaceuticals, as discussed in Chapter One. The introduction describes the gap the guideline seeks to fulfill—that of a risk management framework addressing quality risks that could ultimately impact the patient. (45) Rightly so, ICH Q9 positions the patient at the heart of all QRM activities by acknowledging that, despite the diversity of stakeholder interests (e.g. regulators, industry, healthcare providers, etc.), the interests of the patient are paramount. In practice, industry often uses product quality as a surrogate for the patient, since the impact of quality risks are easier and more scientifically and statistically valid to measure. Provided product quality is defined with an appropriate link to patient, as in Quality by Design (QbD; discussed further in the following section), the application of such a proxy is fitting.

ICH Q9 moves on to immediately dispel a myth that had taken hold in prior industry and regulatory cultures— the concept of zero risk. In older quality paradigms, drug
manufacturers sought to eliminate risk from their products and processes, taking their cue from regulators who implied, through regulatory publications and inspections, that no degree of risk was acceptable. ICH, however, acknowledges that “the manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk.” (45) This perspective shifts the industry-regulator conversation from one of absolutes, where quality was a black and white concept of right and wrong, to one focused on balance, where the level of risk is managed to protect product quality and patient safety. The challenge therefore transitions from achieving an esoteric concept of “perfect” quality to understanding what constitutes acceptable risk and striving to achieve that state—perhaps the most significant paradigm shifts to occur in the history of drug manufacturing and regulation.

Some other misconceptions regarding risk management are addressed in ICH Q9. For example, many associate risk management with the use of rigorous, detailed tools, such as Failure Modes and Effects Analysis (FMEA; one of the most common tools employed by industry). However, Q9 is careful to apply the principles of risk management to the practice of risk management itself; the use of formal or less formal approaches are acceptable, provided the effort is proportionate the risk of the product, process, or system being assessed. (45) This enables industry to embed risk management in all measures of activities, without the need to undertake a formal, resource-intensive exercise. In addition, Q9 is quite clear that the “appropriate use of quality risk management can facilitate but does not obviate industry’s obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.” (45) Compliance with all applicable laws, of course, is mandatory; risk management may not be used to justify non-compliance or to argue
why a specific regulatory requirement need not be fulfilled in a specific instance. Rather, QRM can be used to offer perspectives on how best to comply with statute, and to characterize the aspects of quality that are not specifically associated with compliance. This distinction is discussed in further detail in Chapter Five.

The benefits of a QRM approach are many, ICH Q9 continues. (45) Better assurance of product quality, for example, may be achieved through the proactive identification and avoidance or minimization of quality risks, as well as the identification of sources of variability in the product and manufacturing process that may be targeted for continuous improvement. The decision-making process can be enhanced, as QRM provides a lens through which scientific data and information can be viewed to better weigh options and understand potential outcomes of a given decision. Finally, QRM can “…beneficially affect the extent and level of direct regulatory oversight,” ostensibly by increasing regulator’s trust in a company’s self-awareness through transparency of QRM efforts. (45) The degree to which the patient, through industry, has been able to realize these benefits is further explored in Chapter Four.

Per ICH Q9, the benefits of risk management are to be achieved through the application of a QRM lifecycle, an example of which is depicted in Figure 2-D. The QRM lifecycle is an iterative process consisting of four primary phases: risk assessment, risk control, risk review, and risk communication, each of which is facilitated by the application of risk management tools.11 While ICH Q9 acknowledges that other lifecycle models

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11 Risk management tools and their role in the QRM process will be discussed further in Chapter Eight.
might be used, the majority of industry has adopted the exact lifecycle model described in the guideline.\textsuperscript{12}

Unsurprisingly, the first step in the QRM lifecycle is the initiation of the process. ICH Q9 describes activities that might be performed during this initiation step, including the identification of resources, leadership, and timelines, specifying the problem statement (also referred to as the \textit{risk question}), outlining expected deliverables, and gathering applicable data and information that will serve as inputs into the risk management effort.\textsuperscript{(45)} However, Q9 fails to describe \textit{when} or under what circumstances the QRM process should be initiated; that is, what triggers might exist that should invoke this critical first step. This gap will be discussed in further detail in Chapter Eight.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2d.png}
\caption{Quality Risk Management lifecycle, as per ICH Q9 (45)}
\end{figure}

\textsuperscript{12} An optimized QRM lifecycle, using ICH Q9 and other risk management standards, is proposed and discussed in Chapter Eight.
After initiation, a risk assessment is performed. This phase of the QRM lifecycle seeks to determine which risks associated with the product, process, or system under review are unacceptable—a determination made in three general steps. First, hazards are identified as applicable to the problem statement / risk question (*risk identification*). Each hazard is then analyzed to determine its relative criticality (*risk analysis*), using the risk equation (likelihood x severity = risk) introduced in Chapter One. Finally, the identified and analyzed risks are compared with pre-defined criteria to determine their acceptability (*risk evaluation*). (45) The risk assessment phase of the QRM lifecycle typically draws most heavily upon the use of risk management tools, which allow for a methodical, structured way to identify and analyze risks.

The next phase in the QRM lifecycle, risk control, focuses on reducing risks to an acceptable level.13 This phase is perhaps the most important of the QRM lifecycle, as it is the point in the process in which control strategies are identified, implemented, and continuously improved; risk control is the phase that assures adequate protection of the patient. There are two general activities that occur in risk control; the first being a concerted reduction in risk through the application of risk mitigation techniques (*risk reduction*), and the second including a confirmation that the risk mitigation actions did not adversely affect the overall risk profile through the introduction of new risks or an increase in risk levels, the risks are adequately controlled (i.e. that the risk mitigation actions and other risk controls are effective), and that the resultant risks are therefore acceptable (*risk acceptance*). (45) In the event the risk remains unacceptable following

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13 The name of this phase, as well as the activities that occur within it, reveals an implied principle of QRM: *risks are bad and must be controlled*. This implication is not always the case, as we can learn from other industries and risk management standards; some risks are positive and should be actively pursued rather than reduced, eliminated, or avoided.
risk reduction, the QRM lifecycle returns to the risk assessment phase, allowing the practitioner to repeat the process.

Following risk control, there is an output. Though included in the QRM lifecycle (Figure 2-D), ICH Q9 does not devote any narrative description regarding what such an output or result might entail. Typically, this portion of the lifecycle is interpreted as a documentation point—the point where the results of the risk assessment and risk control outcomes are drafted into a report that describes the risk assessment outcomes (often formatted to align with the risk management tool employed), risk reduction efforts undertaken, and acceptability of the residual risk.

Once risk control is complete and the results have been documented, the risk review phase of the QRM lifecycle begins. The objective of this phase is to ensure that prior activities and associated deliverables remain accurate, relevant, and complete in light of changing conditions. Knowledge gained over the product lifecycle, ongoing activities such as changes to the product, process, or system, unplanned events such as deviations and customer complaints, and changes in the internal and external business and regulatory climate have the potential to impact decisions made in the risk assessment and risk acceptance phases of the lifecycle. (45) Risk review, therefore, entails a periodic or event-driven review of these changes to determine whether the original risk assessment should be updated (as might be the case when new or previously-unrecognized hazards emerge, or the original estimates of likelihood and severity have changed) and whether the acceptability of the risk may be affected as a result. In this sense, ICH Q9 positions risk review as an opportunity to confirm the continued validity of decisions made within the QRM process; it does not address a mechanism to determine whether the QRM process (and encompassing program) itself
has been effective with respect to reducing risk to the patient. This gap is the primary focus of the research effort, as detailed in Chapter Three.

A critical and often overlooked element of the QRM lifecycle is risk communication. Risk communication aims to ensure all applicable stakeholders are aware of risk information, including such aspects as the “…existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality.” (45) Such communication most commonly occurs at the output stage of the QRM lifecycle, leveraging the documentation associated with the risk assessment and control activities as the primary mechanism to communicate; however, risk communication can, and should, occur at other stages of the QRM lifecycle, based on the nature and criticality of the identified risks. Risk communication can occur between varieties of “interested parties”, as depicted in Figure 2-E.

![Figure 2-E: Potential channels for risk communication](image-url)
A significant challenge in the communication of quality risks lies in the relatively limited options for communication between QRM practitioners and decision makers and the patient. Unlike intrinsic risks (such as known adverse reactions) which are typically communicated through product labeling, extrinsic risks, including quality risks, have no defined mechanism for communication. This challenge will be discussed in further detail in Chapter Eight.

ICH Q9 concludes with two annexes: the first describing common risk management tools that may be used to execute the QRM lifecycle, and the second describing potential areas for QRM application within the quality system and product lifecycle. (45) These annexes are of pivotal importance to the effective implementation of QRM and will be discussed in further detail in Chapter Eight.

Despite ICH’s insistence that the Q9 guideline “…is not intended to create any new expectations beyond the current regulatory requirements,” (45) regulatory bodies the world over embraced QRM and have since integrated it at the regional level. Some examples are:

- Inclusion of a new annex to the EU GMPs (Annex 20\(^\text{14}\)), as well as revisions to other directives, annexes, and guidelines to incorporate the principles and practices of quality risk management (46)
- Inclusion of a new annex to the PIC/S GMP guide (also Annex 20) to adopt ICH Q9 for all member countries (47)

\(^{14}\) Annex 20 has since been retired; the QRM requirements have been moved into Chapter 3 of the EU GMPs.
• Publication of the World Health Organization (WHO) guidelines on quality risk management (48)

In addition, QRM has evolved into the foundation of drug development and cGMP platforms, as described in ICH Q8(R2), Q10, and Q11.

2.2.3 Quality by Design: ICH Q8(R2) and ICH Q11

ICH Q8, *Pharmaceutical Development*, (currently in its second revision) outlines the process for the development of new pharmaceutical and biopharmaceutical products, based on the principles of Quality by Design (QbD).\(^\text{15}\) This concept, as described in ICH Q8(R2), brought drug development into the modern era.

In traditional developmental models, a candidate molecule was identified, formulated based on pre-existing knowledge of chemistry and pharmacology (or in the case of biopharmaceuticals, standard cell culture and purification processes), scaled to ensure manufacturing processes could serve anticipated demand, and maintained over the commercial life of the product. In many cases, manufacturers, marketing authorization holders (MAHs), and regulators possessed little knowledge of why the product worked and how the associated manufacturing processes supported the clinical effects of the product. As a result, change was demonized; significant efforts were made to keep the manufacturing process static, since the potential implications of change were largely unknown. Over time, this led to antiquated products and associated manufacturing processes.

\(^{15}\) The concept of Quality by Design (commonly described as building quality into the production of a product, as opposed to Quality by Testing, or relying on the testing a product after production to ensure compliance with specifications) was originally discussed by Joseph Juran in his 1992 book *Juran on Quality by Design: The New Steps for Planning Quality into Goods and Services*. The pharmaceutical industry, regulators, and patients the world over owe Juran a debt of gratitude for his ideas, many of which are only just starting to permeate the fabric of industry. Juran was ahead of time in many respects, and earned his informal title of *quality guru*. 
processes, a general reluctance to harnessing the newest available manufacturing technology, and stalled efforts towards continuous improvement.\textsuperscript{16}

In QbD development models, the emphasis is on understanding the linkages between the product and its clinical effects in the patient, the manufacturing process and the product it delivers, and manufacturing systems and the processes they support. (49) Quality risk management plays a pivotal role in a QbD development model, by helping to improve the breadth and depth of product and process knowledge and enabling this knowledge to serve as an input into manufacturing process design. The application of QbD (and by extension, QRM) ensures that the manufacturing process delivers a product that consistently meets its specifications, that the defined specifications have meaning in a clinical context.

The first step in applying QbD principles to drug development is to define the Quality Target Product Profile (QTPP); that is, the overarching quality characteristics of the product to ensure quality, safety, efficacy, and usability. (49) A list of product attributes can be created from the QTPP and preliminary developmental studies. Through the application of QRM principles and tools, the product attributes can be further triaged to identify those that are critical to the patient (Critical Quality Attributes or CQAs) and those that are not. This distinction allows for the focused application of resources (for example, technical and toxicological studies, preclinical and clinical protocol development, and experimental design) to gain knowledge where it matters.

\textsuperscript{16} Section 2.2.5, describing ICH Q12, discusses the change-averse culture in additional detail.
The identified CQAs are used as the input into manufacturing process development and characterization. Given the large number of variables that exist in even the simplest manufacturing process, the need to distinguish between those variables that are critical to ensure the CQAs are met and those that are not becomes clear. Process parameters or variables that have a direct link to CQAs are deemed Critical Process Parameters, or CPPs, and are identified through the application of QRM. (49)

Manufacturing systems, including facilities, utilities, and equipment, are not discussed in detail in ICH Q8(R2). However, these crucial components are often included in the overarching QbD model, driven by necessity.\(^\text{17}\) Where a manufacturer chooses to extend their development efforts to manufacturing systems, a similar philosophy applies; the equipment, utilities, and facilities are designed to ensure the CPPs of the associated process are sufficiently controlled. (50) The attributes of manufacturing systems that are linked to CPPs are often referred to as Critical Aspects (CAs). The application of QRM to these principles is discussed further in Chapter Eight.

ICH Q11, *Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)*, was published in 2012 and reiterates the general concepts of QbD devised in ICH Q8(R2) as applied to drug substances.\(^\text{18}\) The novel aspects of ICH Q11, when compared with ICH Q8(R2), surround the discussion of how scientific knowledge and QRM can facilitate intended results in a drug development process.

\(^\text{17}\) Given that manufacturing processes are, by definition, run on equipment, using associated utilities, within a specific-purpose facility, the exclusion of this topic from ICH Q8(R2) is peculiar. Other regulatory guidances, such as the 2011 FDA guidance on Process Validation, have since stepped in to fill this gap. (148; 252)

\(^\text{18}\) Drug substances are precursors to drug products, which combine the drug substance with other ingredients to create the finished medicinal product form.
landscape. ICH Q11 directs attention towards a number of applications of QRM in product and process development, including:

- The evaluation of options for the design of the manufacturing process
- The identification of CQAs and CPPs
- The identification of material attributes (e.g. starting materials, raw materials, reagents, etc.) that may have an impact on CQAs
- The identification of functional relationships that link material attributes and process parameters to the CQAs
- The prioritization of attributes or parameters for further study
- The characterization of how downstream processing could affect the acceptability of risk in upstream unit operations (e.g. how impurities present early in the manufacturing process might be acceptable given the process capability of downstream clearance and purification activities), and
- The definition and continuous improvement of the control strategy and associated monitoring program (51)

However, based on the relatively limited descriptions of how to employ QRM in ICH Q11, inconsistencies and confusion may result. For example:

- ICH Q11 notes that “either formal or informal risk management tools… can be used.” (51) This statement could violate the tenants of ICH Q9, which notes that the level of formality of QRM should be commensurate with the level of risk. (45) Indeed, it is difficult to envision how the use of an informal risk tool could be sufficient to characterize the critical elements of a product and process and ensure their control as these are perhaps the highest risk aspects of the product lifecycle.
- ICH Q11 notes that “the risk assessment can also identify CQAs for which there are inherent limitations in detectability in the drug substance (e.g., viral safety). In these cases, such CQAs should be controlled at an appropriate point upstream in the process,” and “when developing a control strategy, a
manufacturer can consider implementing controls for a specific CQA at single or multiple locations in the process, depending on the risk associated with the CQA and the ability of individual controls to detect a potential problem. “ (51) These quotes conflict with the very tenant they seek to explain—that quality cannot be tested into the product, rather it must be built into the product by design. These clauses from ICH Q11 imply that preventive controls should be explored only in the event detection controls are insufficient.

- Example 2 of ICH Q11 illustrates the risk ranking of process parameters, indicating how QRM could be used to propose that low risk parameters be changed without prior regulatory authorization, whereas changes to high risk parameters would be subject to pre-approval. The use of risk ranking is curious in this context, since it is not the level of risk that would enable this determination but rather the severity of the impact a process parameter might have on a CQA—one half of the risk equation. For example, a process parameter would be considered critical in the event it exhibits a strong statistical correlation with a given CQA—that is, if variation in the process parameter has been demonstrated to lead to variation in one or more CQAs. However, risk is not a measure of the likelihood that this correlation exists, but rather the likelihood that unacceptable variation will occur, given the control strategy. The ideal state, of course, is that all process parameters deemed critical based on their functional relationship with a given CQA are well-controlled—meaning, have a low probability of affecting a CQA in the context of the process and associated control strategy. The objective is to ensure that all CPPs are likewise low risk.

It is possible that ambiguities of language and imprecision of examples in the regulatory sphere, such as those illustrated above, could result in a reluctance to apply QRM, or worse, incorrect application. The extent to which this has occurred in the past is explored further in Chapter Five.
2.2.4 QRM as an enabler: ICH Q10

ICH Q10, *Pharmaceutical Quality System*, was published in June 2008 and combined the concepts of QbD, QRM, and GMP into an overarching quality management system to be employed throughout the product lifecycle. This document was developed based on existing requirements and guidance, such as ICH Q7, *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*, ISO 9000, *Quality Management Systems*, and regional GMP requirements. (52) ICH Q10 is often grouped with ICH Q8(R2) and ICH Q9 when describing the fundamental paradigm shift that occurred in the pharmaceutical and biopharmaceutical industries in the late 2000s.

The objectives of ICH Q10 are to:

- Achieve product realization, including the definition and attainment of quality specifications as appropriate for the product and patient
- Establish and maintain a state of control, including the definition of what this state of control entails
- Facilitate continual improvement by enhancing the level of control and knowledge of the behaviors of the product and process interface (52)

In order to facilitate these goals, ICH Q10 reintroduced industry to the product lifecycle and described how four primary quality system elements (process performance & product quality monitoring, CAPA, change management, and management review) should be employed over the various lifecycle stages. A sizable emphasis is placed on

19 Note, the concept of a “state of control” is also detailed in ICH Q8(R2). The concepts put forth in ICH Q8(R2), Q9, and Q10 are synergistic but have slightly different perspectives: ICH Q8(R2) focuses on product- and process-specific control, ICH Q9 focuses on control over risks to patient that might manifest from products and/or processes, and ICH Q10 focuses on supplementary control through management systems, such as change management systems and corrective/preventive action systems. Of course, the totality of the control strategy should include each of these perspectives: process/product control, risk control, and quality system control.
management responsibilities, including ultimate accountability for the quality system and its effectiveness. In addition, ICH Q10 squarely positioned QRM and knowledge management as the two enablers of the quality system. Figure 2-F illustrates the product lifecycle and the elements of the quality system.

Figure 2-F: The Pharmaceutical Quality System (53)

The product lifecycle begins with drug development, a topic discussed in detail in ICH Q8(R2). Following technology transfer, the product is manufactured at commercial scale for sale—products spend the majority of their lifecycle in this stage. The final stage of the lifecycle is product discontinuation, which may be done for any number of (usually business-driven) reasons, such as the expiration of patent protection or the commercial availability of newer products for the target disease indication. Quality risk management, knowledge management, and the four primary quality system elements facilitate all aspects of the product lifecycle, from development through discontinuation.
Risk management principles and practices are embedded in all aspects of the quality system, as illustrated in Table 2-2. The intersection of each quality system element (column) and product lifecycle stage (row) identifies the benefits of applying QRM at that stage.

**Table 2-2: Matrix illustrating the primary functions of QRM at the intersection of quality system elements and product lifecycle stages**

<table>
<thead>
<tr>
<th>Process performance and product quality monitoring system</th>
<th>CAPA system</th>
<th>Change management system</th>
<th>Management review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmaceutical development</strong></td>
<td>Identify critical quality attributes, critical process parameters, preliminary control strategy, and monitoring program</td>
<td>Identify and prioritize sources of variation for further study, correct known issues (reactive risk management), identify and prevent anticipated issues (proactive risk management)</td>
<td>Identify, prioritize, and implement improvements</td>
</tr>
<tr>
<td><strong>Technology transfer</strong></td>
<td>Finalize control strategy and monitoring program</td>
<td>Ensure success of transfer effort through the identification and minimization of the impact of variables between sending and receiving units</td>
<td></td>
</tr>
<tr>
<td><strong>Commercial manufacturing</strong></td>
<td>Ensure continued state of control, identify and implement opportunities for improvement</td>
<td>Identify and prioritize changes to reduce product and process risk, ensure changes are implemented to minimize the introduction of new risk</td>
<td></td>
</tr>
<tr>
<td><strong>Product discontinuation</strong></td>
<td>Support ongoing monitoring of product in the field and evaluation of patient impact</td>
<td>Incorporate learnings from late-stage products to newer products</td>
<td></td>
</tr>
</tbody>
</table>

As an enabler of the quality system, QRM is the “engine” that drives the quality system over the product lifecycle, transforming information into knowledge and facilitating the
identification of opportunities to improve the product and associated processes to better serve the patient.

2.2.5 Lifecycle Management: ICH Q12

In September 2014, ICH announced a new effort to expand the portfolio of Quality guidelines with the addition of ICH Q12, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. In the final concept paper for this guideline, ICH acknowledged that, true its original name of the International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, the majority of deliverables had focused on pre-market requirements. There was a clear need, however, to extend the scope of the group into later stages of the product lifecycle, since “the envisioned post-approval ‘operational flexibility’ [outlined in ICH Q8(R2) through Q11] has not been achieved.” (54). In order to better facilitate this objective, the Q12 guideline will attempt to:

“…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 changes.” (54)

ICH later changed its name to the International Council on Harmonization to better align with the newly-envisioned scope of influence. (55)
The announcement of this effort was lauded by industry, as the challenges associated with regional differences in post-approval change management are many. (56) Each country has a distinct set of requirements and expectations regarding how such changes may be handled, whether through a firm’s change management program within their quality system (with post-implementation communication to regulators), or through rigorous pre-implementation regulatory approval. This poses logistical difficulties, as companies must juggle inventory manufactured with different variations of change, directing product to specific markets based on the CMC approval status of the applicable regulatory authority. (57) This often requires firms to continue manufacturing product under an older manufacturing scheme to ensure consistent supply of product to patients under the jurisdiction of regulatory bodies requiring pre-implementation approval of the change. (58) Because of this, many have noted that the global complexity associated with manufacturing change has discouraged innovation and continual improvement.

Among other benefits, ICH Q12 is expected to more clearly link change management with QRM and knowledge management, the two enablers of the quality system as described in ICH Q10. (59) In addition, minimization of the regulatory hurdles associated with product and process lifecycle management and post-approval change management should spur renewed focus on improvement and innovation. ICH Q12 is targeted for finalization in November 2017 and is eagerly awaited by industry and regulators alike. (60)
2.3 QRM guidance from industry, for industry

Following the publication of ICH Q9, industry eagerly embraced the opportunity to share ideas and best practices related to QRM. The cadence of publication steadily increased as ICH Q8(R2), ICH Q10, and ICH Q11 emerged, as thought leaders sought to provide practical guidance to industry on the application of QRM. As outlined in the literature map for this chapter (Figure 2-A), this section will focus on selected publications addressing general, rather than specific, applications of QRM.

The first book published on the topic of QRM was one by renowned quality expert James Vesper in June 2006, one year following the publication of ICH Q9. Entitled *Risk Assessment and Risk Management in the Pharmaceutical Industry: Clear and Simple*, the book posits risk management is nothing new; people (and industry) are exposed to and must manage risk every day, whether they are exposed to hazards during a daily commute to work or through the manufacture of sterile, life-saving medicines. Through this simple comparison, Vesper dispels any anxiety-provoking stigma that might accompany the introduction of a new quality management tool and made the concepts of QRM more accessible to and achievable by the reader. This pragmatic tone quickly became the *modus operandi* within industry literature, as many subsequent publications adopted a case study approach in lieu of rigorous philosophical discussion on the principles and application of QRM.

Vesper’s book describes the objectives of and process for quality risk management, but devotes much of the text to a discussion of risk tools and assessment methods. While this was certainly appropriate given the low level of QRM knowledge within industry at the time, combined with general (albeit misguided) perceptions that risk assessment
was synonymous with risk management, the emphasis on risk tools is now viewed as a very narrow scope indeed.

In 2012, the Parenteral Drug Association (PDA) published the first (and only) industry whitepaper on the general principles and best practices associated with a QRM program, Technical Report No. 54, *Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations*. In addition to expanding upon ICH Q9 to offer additional guidance on QRM implementation, this technical report expands the body of knowledge by introducing industry to three key concepts to be applied in QRM: risk maturity, the formality spectrum, and human heuristics.

PDA chose to begin the technical report with an introduction of risk maturity, which serves as the foundation of this research effort and is discussed in detail throughout this thesis. A brief review of where QRM should be applied throughout the product lifecycle, as described in ICH Q8(R2), Q9, and Q10, is offered, followed by a discussion of the different types of risk management: proactive and reactive. This distinction is particularly important but had not been given much attention in the ICH guidelines; the inclusion of this concept in the PDA technical report sets the tone for future discussions within industry. In addition, PDA proceeds to examine the role of

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20 While other whitepapers on QRM exist from PDA and its peer, the International Society for Pharmaceutical Engineers (ISPE), those are focused on providing an overview, typically in case study format, of how QRM can be applied to a specific problem or technology platform. For example, PDA’s 2008 *Technical Report No. 44, Quality Risk Management for Aseptic Processes* reviews QRM as applied to product sterility; ISPE’s 2010 Baseline Guide *Risk-based Manufacture of Pharmaceutical Products* addresses only cross-contamination risks only; and ISPE’s 2011 *Science and Risk-based Approach for the Delivery of Facilities, System, and Equipment* and *Applied Risk Management for Commissioning and Qualification* focus solely on QRM application within engineering and qualification efforts. The specificity and narrow scope of these whitepapers rendered them inappropriate for this chapter, although the implications of these documents (and the targeted risk management mindset they represent) is addressed in Chapters Five and Eight.
governance in a QRM program, including organizational and managerial aspects that are pivotal to the success of QRM; not least of these being transparency in communication throughout all levels of a company. (62) This success factor has been identified as an ongoing challenge, discussed further in Chapters Seven and Nine.

The PDA technical report also explores the concept of proportionality of risk management, explaining the intent behind the clause in ICH Q9 that efforts in QRM should be commensurate with the level of risk. (45) PDA relates proportionality to various risk tools and the rigor with which they should be applied. For example, PDA suggests that more formal tools, such as FMEA or HACCP, should be applied to more critical and complex systems and leverage expert knowledge from a risk facilitator and curated QRM team to execute the assessment, while less formal tools such as risk ranking need not employ the services of QRM experts in all cases. PDA points out that formality should not be considered a dichotomy (i.e. either formal or informal), but rather is a spectrum that allows for various combinations of rigorous methods, techniques, documentation options, and expertise to be employed as appropriate for the risk question. (62)

The concept of human heuristics, as applicable to QRM exercises, is likewise reviewed in PDA’s Technical Report No. 54. The influence of human heuristics on decision-making processes was first identified by decision science gurus Daniel Kahneman and Amos Tversky, whose work earned a Noble Prize in Economics in 2002.21 PDA borrowed both from Kahneman/Tversky and from the Pharmaceutical Regulatory

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21 While Kahneman and Tversky considered themselves cognitive psychologists, they are credited with establishing a new field of study known as behavioral economics, for which the Nobel Prize was awarded. Though the Prize went to Kahneman, it is broadly acknowledged that Tversky would have been a co-recipient had he been alive to receive it. (119)
Science Team’s (PRST) own Dr. Kevin O’Donnell, who made the critical linkage between Kahneman’s work and QRM in 2010 through the publication of a two-part article addressing subjectivity and uncertainty in QRM exercises. (63) (64) Human heuristics are cognitive “shortcuts” that are used when judgments are made in the presence of uncertainty; colloquially these are referred to as “rules of thumb.” Heuristics have the potential to adversely affect the validity of risk analyses and risk acceptance decisions, as the estimation of risks and their acceptability to the patient can be greatly influenced by cognitive shortcuts at the expense of scientific knowledge. PDA called attention to this phenomenon where other sources had neglected it; the importance of human heuristics in QRM marks this as a breakthrough.

PDA Technical Report No. 54 was one of the earliest documents of its kind, focused on the establishment of a QRM program to be integrated and applied within the product lifecycle. Because of this strategic perspective and the best practices offered within the text, this technical report has become one of the most widely referenced treatises on the enabling function QRM plays in an effective quality system.

*Risk Management Applications in Pharmaceutical and Biopharmaceutical Manufacturing*, edited by Mollah et al and published in 2013, offers a modern and much more sophisticated treatise on QRM, including chapters on philosophical, academic, and statistical topics that enabled a more comprehensive understanding of the benefits and concepts underpinning QRM. (65) The book is comprised of chapters on various QRM topics, compiled from myriad QRM experts; this book therefore represented the perspectives of thought leaders on QRM at the time.
Mollah et al provide a succinct business case for the application of risk management for quality improvement before delving into how various risk management tools can support the overarching QRM lifecycle. Acknowledging the difficulty of providing discrete “rules” around the use of particular methodologies at the expense of others, Walker and Busmann compare the advantages and limitations of the basic QRM toolkit (e.g. those summarized in Annex I of ICH Q9). (66) A noticeable gap in the relevant chapter surrounds tool selection—how to select the best fit risk tool for a particular circumstance and risk question. This gap will be discussed further in Chapter Eight.

Long offers his expertise on regulatory expectations of QRM, including common misunderstandings and pitfalls associated with risk implementation, in his chapter “Risk Management: Regulatory Expectation, Risk Perception, and Organizational Integration.” (67) Some instances of QRM misuse as described by Long include:

- Lack of QRM usage (not assessing the risk to patient or product quality where warranted by an event or circumstance)
- Improper implementation of QRM (lack of evidence supporting risk-based decisions, lack of sufficient product and process understanding)
- Variable risk tolerance (deeming a given risk management “acceptable” in some instances but not others, with no clear explanation)
- Use of QRM to justify an expected outcome (“reverse engineering” a risk assessment to justify a previously-determined decision or outcome) (67)

Perhaps the greatest contribution of Mollah et al’s book is Long’s chapter on probability estimates and statistical techniques as they relate to QRM exercises. (68) Despite the fact that probability is a full 50% of the risk calculus (likelihood x severity = risk), there are very few sources available to industry QRM practitioners that explore this topic in
Long addresses this topic head on, explaining general principles of probability, the roles of uncertainty and heuristics in estimating probability, and the benefits of moving towards more quantitative, data-driven assertions to support the validity of QRM outcomes. Indeed, as this researcher explored in a recent paper, industry commonly confuses risk management tool categories (qualitative vs. quantitative) with the application of quantitative risk analysis efforts, using actual probability estimates grounded in scientific data. Long’s direct inquiry into the relationship between statistics and QRM makes a critical connection that is often overlooked by industry practitioners.

Based on the depth of discussion to all manners of QRM topics, *Risk Management Applications in Pharmaceutical and Biopharmaceutical Manufacturing* serves as a rich source of knowledge that can enhance the level of expertise of its readership, contributing to general increases of QRM maturity within industry.

Several key lines of inquiry were extracted from the general literature review to serve as focus areas throughout the research effort. These include:

- The need to concentrate on program effectiveness in reducing risk to the patient when evaluating QRM maturity
- The need to link QRM with medicinal product development and characterization efforts (as in ICH Q8(R2) and Q11), as well as the pharmaceutical quality system (as in ICH Q10)

22 The lack of attention paid to statistical consideration in risk analysis is particularly disappointing in the pharmaceutical and biopharmaceutical industries, which are grounded in sound science, the scientific method, and associated mathematical and statistical ways of analyzing and understanding data. Given the fact that, as Kahneman noted, people are poor “intuitive statisticians,” (119) the importance of connecting QRM to objective and rigorous sources of knowledge is essential.
The need to ensure that key concepts that influence QRM outcomes (or might degrade the integrity of the QRM process) are integrated within the overarching QRM program. Such concepts include:
  - Risk tool selection, including the formality spectrum and advantages/limitations of common risk management tools

Chapter Three of this thesis further details how these earmarked themes were incorporated into the overarching research effort.
3 Chapter Three: The Research Approach

This research study investigated the concept of effectiveness in quality risk management in managing risk to the patient, in an effort to define a mature state of QRM that can be used by industry to gauge their current level of QRM implementation and progress on the path towards excellence. Because *effectiveness* is a rather intangible concept, stemming from combinations of business practices (processes), attitudes and behaviors of those employing these processes, and the organizational culture within which the people and processes operate, the research is primarily qualitative in nature, although quantitative methods were also used. Mixed methods of research were employed throughout the research effort, as best suited for the particular aspect of the research question.

3.1 The researcher’s context

3.1.1 The researcher’s worldview

It is necessary for any researcher to examine their own philosophical worldviews prior to commencing a research effort, as these represent the lens through which the research is conducted and analyzed. While these endeavors have many labels, including paradigms, ontologies, and epistemologies, the researcher has selected the term *worldviews* so as to minimize any potential for *reductio ad absurdum*. Many academics undertaking a similar effort may position this process as one of selection—implying that a particular worldview can be selected based on its appropriateness for the topic under review. This researcher disagrees with this general approach, believing that each
individual inherently possesses a natural inclination towards one worldview or another. While worldviews may change over the course of a lifetime, they are relatively fixed within the finite span of a research effort. Therefore the goal of this section is to disclose, rather than to describe the selection of, this researcher’s viewpoint.

The best-fit worldview to reflect this researcher’s philosophical inclinations is *pragmatism*. Pragmatists are not committed to any one idea of reality, be it an external reality or one encased within the mind; the hallmark of pragmatism is that philosophy, and the related concepts of reality and the nature of knowledge, is largely esoteric and therefore irrelevant in any tangible sense. (70) This researcher agrees that an exploration of the nature of reality and what can be known is quite interesting, but of little consequence with respect to the conduct of academic and industry research and the resultant research outputs. Pragmatists are primarily concerned with finding what works for a given problem, rather than aligning it with one particular ontological position— this researcher agrees that “truth is what works at the time.” (71) With regard to academic inquiry, pragmatism acknowledges that research occurs in a given context, and therefore must be interpreted in light of that context. (71) For example, if complete certainty regarding the future and complete knowledge of the behavior of process variables in a system, for a given product, could be known, the field of risk management need not exist. As a pragmatist, however, the researcher asserts that these two conditions are not met (irrespective of whether they are theoretically plausible), and therefore risk management principles and practices are necessary in order to progress pharmaceutical and biopharmaceutical operations and regulatory science in any meaningful sense with respect to the patient. The *context* in which this research is conducted is one of uncertainty and incomplete knowledge.
Mixed methods research, as discussed in section 3.4, is particularly well-suited for a pragmatic worldview, since this methodology allows for a large toolkit of different methods from which the researcher can choose to best serve the research goals. This also enables the research process, as well as the research outputs, to have an impact on industry practitioners, as engaging these stakeholders in a variety of ways stimulates thinking and can effect change. Similarly, a pragmatic worldview allows the research to focus on the development of tangible work product that can be applied and used by stakeholders, the primary driver behind this researcher’s efforts.

### 3.1.2 Insider perspective

The researcher’s desire to deliver a positive impact to industry is driven by her insider perspective. With fourteen years in industry (as of this writing), the researcher is equipped with a deep knowledge of industry practices and challenges, and has had sufficient opportunity to see quality-based fads rise and fall without gaining any long-term purchase, consuming an extreme amount of resources and intellectual capital in their implementation only to see minimal benefits be realized as a result. Given the criticality of the topic at hand and the amount of time, effort, and passion necessary to advance the research effort, the researcher sought to simultaneously embark on a rigorous academic inquiry and develop meaningful, tangible outputs to address the needs of industry practitioners. As such, the researcher developed the overarching research design with these goals in the forefront.

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23 While some of these efforts, such as the principles and tools derived from Lean Manufacturing and Six Sigma, remain in force in pockets or through faint echoes in other formats, a simple search of the literature provides evidence of the temporal boundaries of these quality improvement schemes.
The researcher’s own experiences within quality control and quality assurance have led, ultimately, to a fervent enthusiasm for quality risk management. An early career in various quality functions, including microbiology, product release, change control, and deviation and CAPA management, led to a host of frustrations. A small error in aseptic technique could contaminate thousands of doses that would have otherwise treated a similar number of patients. A drug shortage situation could lead to deaths of many, while the product awaits investigation into ultimately inconsequential deviations. Seemingly minor changes, when implemented, could initiate a domino effect on a manufacturing process significant enough to render it useless. It was only with an initial foray into QRM that the researcher learned that such frustrations are both predictable and preventable. The only obstacle standing in industry’s way was a map to guide them there.

Insider research has both advantages and disadvantages, and inevitably lends color to the research effort. Advantages of the insider perspective include:

- **Knowledge**: Pre-existing knowledge of the research topic can shorten the time needed for the researcher to orient herself, while allowing for a depth of interpretation that might otherwise be absent.

- **Interaction**: Researchers who are familiar with cultural and linguistic norms in a given topic or within a given social group enable a more natural interaction with research subjects, which is particularly useful when qualitative research methods are employed.

- **Access**: Researchers who are considered part of a given social group may enjoy easier access to thought leaders within the group for the purposes of the research. (72)
Disadvantages of insider research include:

- **Excessive subjectivity**: Insider status can serve as an impediment to objectivity, as data is analyzed through an existing contextual framework that may be too narrow.
- **Bias**: “researcher bias in this context would refer to the process whereby the researcher’s personal beliefs, experiences, and values influence the study methodology, design, and/or results.”

The researcher acknowledges the disadvantages associated with an insider perspective, particularly those associated with bias. The researcher has identified and discloses one such bias that is present in the research process and outputs; namely, the underlying assumption of the research question: *QRM works*. Of course, was this assumption to be false, it is unlikely that the international regulatory community and industry at large would have channeled so much energy into encouraging its adoption. While this fundamental assumption has been retained, the researcher has taken many pains to minimize any potential bias in the research methods, construction of benchmarking surveys and questionnaires, with all involved research subjects, and in the interpretation of the results.

### 3.2 Ethics and privacy

The research plan received approval from the Research Ethics Committee on April 14, 2015. The research was conducted in accordance with DIT’s Ethical Guidelines.

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24 Of course, some sources claim that in certain circumstances, bias may be an advantage and should therefore not be feared, since “the insiders’ biases may be a source of insight as well as error.”

25 The researcher must likewise acknowledge that even this assumption should be challenged. Over the course of the researcher, it became increasingly clear that there is currently no systematically-gathered evidence to support this assumption. While personal experience and a wealth of anecdotes provide support, Chapter Eleven of this thesis suggests that widespread evidence be gathered to, finally, confirm or refute this assumption.
The researcher has not (and will not) have any power over any of the involved research subjects, each of whom agreed voluntarily to participate. Each subject has been (and will continue to be) provided with an appropriate brief regarding the purpose of the research, expected time commitments, and anticipated outcomes, and provided consent in a documented format. Where requested, each subject’s identity was/will be kept completely confidential, with associated data encoded to eliminate any traceability to a particular individual.

A Conflict of Interest was disclosed as part of the ethics package to ensure transparency with regard to the researcher’s current employment in the pharmaceutical industry.26 The researcher’s employers had no access to the research in advance of publication, so no competitive advantage was available.

All raw and analyzed data is kept in an electronic format, encrypted via Symantec’s Endpoint Encryption software,27 and stored on a personal password-protected computer. The one exception to this are hard-copy consent forms which are stored in a designated, locked file cabinet located in the researcher’s home. All efforts were made to ensure that research subjects’ rights and privacy were maintained, and all data was secured.

Ethical approval was sought and granted on April 21, 2015.

26 Refer to section 3.1.2 for additional information on the insider perspective.
27 Refer to https://www.symantec.com/products/information-protection/encryption for additional information. Please also note that software support is purchased through an annual subscription which is being sustained by the researcher through the life of the research effort, which will continue until achievement of the PhD award or cessation of the program, at which time all electronic and hard copy data will be destroyed.
3.3 A brief history of the research question

The original research proposal, as included in the research application and registration package in June 2014 (74), cited the following primary hypothesis:

“Industry has failed to fully embrace the principles and processes outlined in ICH Q9. QRM is absent or has been misapplied in multiple areas of the quality system for the majority of pharmaceutical and biologics manufacturers.”

Of course, merely confirming or refuting this hypothesis would be an incomplete research inquiry, with little ability to effect change within the pharmaceutical and biopharmaceutical industries. As a result, a secondary hypothesis was proposed, as follows:

“A primary contributing factor to the current state of QRM in industry is the lack of intra- and inter-industry benchmarking with respect to the constitution of an effective QRM program. Without a successful model to emulate, firms struggle to implement a holistic program to enable their quality management system in the spirit of ICH Q9 and Q10.”

At the time of writing the confirmation report in the fall of 2016, the researcher had progressed in her thinking and elected to refine the initial hypotheses into a research question, as follows:

“Has industry achieved a state of effective risk management, whereby QRM is conducted in an efficient manner and continually adds value to operational and quality processes in the manufacture of pharmaceutical and biopharmaceutical
products? What does effective and efficient quality risk management look like, and how can it be achieved?”

This research question more sufficiently phrased the researcher’s trajectory at that stage of learning, with the original intent of risk maturity preserved, yet re-envisioned as a function of effectiveness, efficiency, and value.

However, as time passed, the researcher again began to rethink the true objective of the research. Over the course of the three-year research effort, this researcher has been fully absorbed into the academic and industrial world of QRM. Thought leaders and experts have spoken at length about QRM at conferences, sharing their opinions in open venues and in peer-reviewed journals, espousing the need to apply QRM to a multiplicity of topics. Regulators, similarly, have increased focus on QRM with a litany of new regulation, guidance, and inspection techniques. Despite this increased attention, the researcher became increasingly dissatisfied with the way the conversation was evolving—while there was more discussion around “doing QRM,” there was less around managing risk to the patient. As discussed in the introductory literature review (Chapter Two), very few sources address the fundamental question of how QRM should be used to serve the patient. Indeed, there are no such sources that look holistically a comprehensively across a QRM program, including the governance, process, and people-related aspects that are essential to build and sustain a state in which risks to the patient are effectively managed.

And thus the third and final revision of the research question crystallized:

“How can industry recode QRM to better manage risks to the patient?”
3.4 Research design, methodology, and methods

Based on the research question discussed in the prior section, the research design followed a phased approach to encompass the logical progression of research topics. The first phase focused on characterizing the current state of the industry with regard to reaping the benefits of better patient protection. The second phase sought to understand the ways in which QRM is being used to try to achieve that benefit. The third phase focused on better defining a mature state of QRM to realize the benefit, as well as providing tangible solutions to help industry measure and progress on the path towards the ideal.

Table 3-1: Research design, methodology, and methods

<table>
<thead>
<tr>
<th>Research Phase</th>
<th>Objective</th>
<th>Methodology</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Characterize the current state of industry with regard to patient benefit realization</td>
<td>Quantitative</td>
<td>Literature review / data analysis</td>
</tr>
<tr>
<td>2</td>
<td>Characterize the current state of industry with regard to QRM implementation</td>
<td>Explanatory sequential mixed methods</td>
<td>Literature review / data analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Structured benchmarking survey</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Literature review</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Philosophical dialogues</td>
</tr>
<tr>
<td>3</td>
<td>Define how QRM implementation might better protect the patient</td>
<td>Exploratory sequential mixed methods</td>
<td>Literature review</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Philosophical dialogues</td>
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<td></td>
<td></td>
<td></td>
<td>Semi-structured interviews</td>
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<td></td>
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<td>Transcript analysis</td>
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<td></td>
<td></td>
<td></td>
<td>Pilots /case studies</td>
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</tbody>
</table>

Mixed methods research was chosen as the most suitable research methodology to employ within the overarching research design. Specifically, an overarching *embedded mixed methods* approach was employed. This methodology includes combinations of
quantitative, explanatory sequential mixed methods and exploratory sequential mixed methods research techniques in an iterative framework. (71) Quantitative research is primarily focused on data analysis, and where therefore chosen for the Phase 1 research. Explanatory sequential mixed methods begin with quantitative research, followed by qualitative techniques to support interpretation (71); this methodology was chosen for the second phases of the research to better gauge the current level of QRM adoption. Exploratory sequential mixed methods progress in opposite of explanatory sequential mixed methods; that is, qualitative methods are employed at first, followed by a quantitative inquiry to facilitate interpretation. (71) Exploratory sequential mixed methods were used in the final phase of the research.

As discussed above, Phase 1 sought to characterize the extent to which industry (and the patient) have realized the benefit of improve product quality and patient protection through quantitative research approach. Figure 3-A outlines the research method employed during Phase 1.

![Figure 3-A: Quantitative approach used in the Phase 1 research](image)

Phase 2 of the research used an explanatory sequential mixed methods approach to characterize the current state of QRM implementation in the pharmaceutical and biopharmaceutical industries. Figure 3-B illustrates the research methods employed during Phase 2.
Phase 3 of the research involved a synthesis of the learnings from the prior two research phases as well as some additional methods in order to define an ideal state of QRM. Because of the iterative nature of prior and new qualitative methods and the quantitative pilot/case study employed in Phase 3, an exploratory sequential mixed methods approach was used, as illustrated in Figure 3-C.

3.5 The research effort

Prior to initiating the research, the researcher had published two peer-reviewed articles on QRM and presented two industry conference sessions. While these work products were not specifically related to a formal research effort with a defined hypothesis, the
covered topics added to the existing body of knowledge on QRM and the opportunities to socialize ideas within industry led to the establishment of positive professional relationships with QRM thought leaders.\textsuperscript{28} These publications piqued the researcher’s interest in pursuing a more rigorous form of inquiry, and a research abstract and application to DIT’s graduate program was submitted.

3.5.1 Summary of the Phase 1 Research

The research commenced in June 2014, immediately following approval of the research proposal and admission into the graduate program. The initial focus was to develop an understanding of whether QRM had yielded some of the benefits listed in ICH Q9—in particular, higher quality products and resultant patient protection. To determine whether drug product quality had improved since the inception of ICH Q9, an analysis of quality-related recalls and critical quality defects in the US and Ireland was conducted to identify any applicable trends that may cast light on the research question. The researcher simultaneously began work on the first stage of the Phase 2 research to evaluate potential improvements in compliance and QRM implementation through a review of warning letters (from FDA) and inspection observations (from HPRA), as described in section 3.5.2.

In December 2014, the researcher was contacted by the Institute of Validation Technology (IVT) and invited to serve as chairperson of the institute’s first Quality Risk Management conference. The researcher coordinated known industry experts to participate as speakers and suggested QRM-related topics that were suitable for the

\textsuperscript{28} These relationships have proven beneficial to the research, in line with the interaction and access advantages of insider research described in section 3.1.2.
target attendees. The conference was held in Orlando, Florida (US) in January 2015 with a small but meaningful enrollment of approximately eighty industry practitioners. The researcher provided opening remarks, followed by a presentation of the initial quality defect and compliance observation data analysis discussed above. The researcher also presented two additional topics, on risk-based impact assessment and the creation of custom QRM tools. Also in January 2015, IVT arranged for peer review of a paper on the quality defect and compliance observation analysis, which was ultimately published in the *Journal of Validation Technology* (one of two journals published by IVT).

Chapter Four summarizes the data and analysis for the Phase 1 research.

### 3.5.2 Summary of the Phase 2 Research

Following the completion of the Phase 1 research, the researcher began inquiry into the current level of QRM implementation, with a research plan that included a literature review and data analysis, an industry benchmarking survey, a qualitative literature review, and philosophical dialogues. At this time, the researcher was invited to participate in a PDA task force, responsible for the creation of a technical report on the application of quality risk management to the design, delivery, validation, and use of manufacturing systems, inclusive of facilities, utilities, manufacturing equipment, and similar support systems.29

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29 Participation on this task force proved to be a multi-year effort. The deliverable from the task force, PDA Technical Report No. 54-5, *Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems*, was published in May 2017.
In July 2015, the researcher was selected for the PDA Volunteer Spotlight. This honor is granted to one innovative, active participant in the group each month, who is highlighted in a full-page interview in that month’s issue of the PDA Letter. The researcher was chosen based on her work with the PDA task force described above.

In order to reach a larger target audience and to enhance access to industry experts for the Phase 2 and 3 research the researcher developed a proposal for a research collaboration with PDA. The PDA was selected by the researcher for this collaboration effort based on a number of factors, including the PDA’s reach (as of this writing, PDA has over 10,000 members worldwide; (75)), members’ expertise and innovation in the area of QRM, and the historical relationship between the researcher and the organization.

The DIT/PDA collaboration proposal outlined the research objectives, portions of the research plan which were intended to be included in the collaboration, anticipated timelines, and benefits that the collaboration would yield to industry and regulatory science. The proposal clearly identified that the research and all deliverables would be conducted by the researcher, primarily leveraging the PDA QRM Interest Group and other volunteers as research subjects. The proposal was brought to vote with the PDA’s Regulatory Affairs and Quality Advisory Board, and received unanimous approval in August 2015. The research collaboration was socialized through a talk at the PDA/FDA Joint Regulatory Conference in September 2015, and in an article in the PDA Letter the following month.

Having secured access to a large potential research subject pool, Phase 2 commenced with a preliminary draft of an industry benchmarking survey designed to elicit both
opinions and current practices related to QRM from volunteer respondents. The survey was developed in accordance with current standards of survey research, (76) to:

- obtain respondent consent prior to completion of the survey,
- ensure only the target population could respond (industry practitioners who could represent their current experience in a particular company, rather than consultants, for example),
- minimize potential ambiguity in the questions,
- mask any potential researcher bias that may have inadvertently colored the question, and
- have a clear and logical flow

The draft survey was review by peers from the PRST prior to being coded in the SurveyMonkey online software application.30

The QRM benchmarking survey opened on October 1, 2015. An email was distributed by PDA to its membership list to solicit participation. The survey was originally scheduled to close on December 31, 2015, however the response period was extended through January 31, 2016 at the request of PDA Japan, who expressed particular interest in understanding any potential regional differences with regard to QRM adoption. A total of 230 responses were received, including (approximately) 144 complete responses. Preliminary results (addressing trends and themes for industry as a whole) were presented at the PDA Annual Meeting in March 2016; the presentation was subsequently featured in The Gold Sheet, an electronic periodical highlighting current

30 SurveyMonkey employs the latest security technology and encrypts each respondent’s personal information to assure privacy. The researcher’s SurveyMonkey account was password protected so that no person other than researcher had access to the survey results prior or subsequent to analysis and presentation.
topics in pharmaceutical and biopharmaceutical quality and regulatory affairs and was recently published in the *PDA Journal of Pharmaceutical Science and Technology*.

While the benchmarking survey was ongoing, the literature review commenced. Because the goal of Phase 2 was to characterize the current state of industry with regard to QRM, literature was selected based on two criteria:

- Topic under consideration addressed QRM principles, practices, or a portion of the QRM lifecycle
- Content directly related to the pharmaceutical or biopharmaceutical industry (either through publication by a regulatory agency, industry group such as PDA, ISPE, or IVT), or in an industry-targeted journal or periodical)

Peer-reviewed publications were targeted where possible, however presentation materials and opinion pieces were reviewed as well, provided these had the potential to reach the target group (industry professionals) based on the conference at which they were delivered or periodical in which they were published. Literature was selected through a systematic review of all sources identified in Table 3-2. An overview and critical analysis of the literature is summarized throughout this thesis.
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<thead>
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<th>Issuing Organization</th>
<th>Data Type</th>
<th>Publication frequency</th>
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<td>FDA, EMA, ICH</td>
<td>RSS Feeds</td>
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<td>Ad hoc</td>
</tr>
<tr>
<td>BioProcess Online</td>
<td>Jameson Publishing</td>
<td>Subscription service</td>
<td>Ad hoc</td>
</tr>
<tr>
<td>Life Science Leader</td>
<td>Jameson Publishing</td>
<td>Subscription service</td>
<td>Ad hoc</td>
</tr>
<tr>
<td>Med Device Online</td>
<td>Jameson Publishing</td>
<td>Subscription service</td>
<td>Ad hoc</td>
</tr>
<tr>
<td>GMP Trend Report</td>
<td>GMP Trends, Inc.</td>
<td>Subscription service</td>
<td>2x Month</td>
</tr>
<tr>
<td>The Gold Sheet</td>
<td>Informa</td>
<td>Subscription service</td>
<td>Monthly</td>
</tr>
<tr>
<td>Life Science Leader</td>
<td>Jameson Publishing</td>
<td>Industry publication</td>
<td>Monthly</td>
</tr>
<tr>
<td>Pharmaceutical Technology</td>
<td>Advanstar</td>
<td>Industry publication</td>
<td>Monthly</td>
</tr>
<tr>
<td>Biopharm International</td>
<td>Advanstar</td>
<td>Industry publication</td>
<td>Monthly</td>
</tr>
<tr>
<td>Pharmaceutical Executive</td>
<td>Advanstar</td>
<td>Industry publication</td>
<td>Monthly</td>
</tr>
<tr>
<td>PDA Letter</td>
<td>PDA</td>
<td>Industry publication</td>
<td>10x year</td>
</tr>
<tr>
<td>Pharmaceutical Engineering</td>
<td>ISPE</td>
<td>Industry publication</td>
<td>Bi-monthly</td>
</tr>
<tr>
<td>PDA Journal of Pharmaceutical Science &amp; Technology</td>
<td>PDA</td>
<td>Peer-reviewed journal</td>
<td>Bi-monthly</td>
</tr>
<tr>
<td>Journal of GxP Compliance</td>
<td>IVT</td>
<td>Peer-reviewed journal</td>
<td>Bi-monthly</td>
</tr>
<tr>
<td>Journal of Validation Technology</td>
<td>IVT</td>
<td>Peer-reviewed journal</td>
<td>Bi-monthly</td>
</tr>
<tr>
<td>PDA Technical Reports</td>
<td>PDA</td>
<td>Peer-reviewed whitepapers</td>
<td>Ad hoc</td>
</tr>
<tr>
<td>ISPE Baseline Guides</td>
<td>ISPE</td>
<td>Peer-reviewed whitepapers</td>
<td>Ad hoc</td>
</tr>
<tr>
<td>Regulation and regulatory guidance documents</td>
<td>FDA, EMA, ICH</td>
<td>Authoritative</td>
<td>Ad hoc</td>
</tr>
</tbody>
</table>

In addition, the researcher commenced philosophical dialogues with industry practitioners and QRM experts. These dialogues spanned a number of topics, including
QRM best practices, obstacles preventing a more mature application of QRM, specific challenges and frustrations experienced by industry, and feedback on the industry benchmarking survey. The researcher leveraged all available forums to conduct these industry consultations, drawing heavily upon industry conferences at which large numbers of experts were present. The use of active listening proved invaluable in the Phase 2 research, and continued through the final stage of the research.

Within Phase 2, the researcher served as guest editor for a special double issue of the *Journal of Validation Technology*, published in December 2015. This issue, dedicated to quality risk management, featured peer-reviewed articles written by industry thought leaders and current and former regulators and marked the ten-year anniversary of the publication of ICH Q9. The key theme of the issue was how industry can improve current QRM practices to achieve better results. In addition to compiling the issue and working with authors to position the work within the overarching theme, the researcher contributed two articles to stimulate industry thinking on important but neglected topics. These articles, as well as those of the other contributors, became part of the literature review in Phase 2 and Phase 3.

Finally, the literature review was extended to other industries in which risk management techniques have proven effective; namely, the medical device, aerospace, and nuclear power industries. Chapter Six is fully dedicated to exploring this topic.

### 3.5.3 Summary of the Phase 3 research

Phase 3 of the research focused on defining an optimal state where QRM can be applied to better manage risks to the patient. Specifically, this phase entailed the development
of a deep understanding of the ways in which QRM should be applied to minimize emphasis on the risk management activities themselves while maximizing the benefits to the patient. Necessarily this involved the exploration into risk maturity and QRM best practices as originally envisioned in the research proposal, and involved the synthesis of Phase 1 and 2 learnings with a more sophisticated and precise research plan.

The three qualitative research methods (literature review, philosophical dialogues, and expert interviews/transcript analysis) were iterative in nature, as learnings from each inspired further research from the others. The design of the semi-structured interviews was based upon specific areas of inquiry deemed necessary by the researcher to fully answer the research question, as follows:

1. In your opinion, how far has the industry comes towards achieving the vision and benefits of QRM as outlined in ICH Q9 and Q10?

2. What are the main challenges you believe industry must overcome in order to more fully achieve those benefits?

3. What aspects of the quality system do you think require more attention and improvement?

4. What best practices would you say are currently being used in QRM?

5. What aspects of the quality system do you think are currently well-addressed through QRM programs?

6. In your opinion, what would be some of the characteristics of a mature QRM program?

7. In your opinion, what are some of the characteristics of an immature QRM program?
8. What behaviors of industry personnel do you feel must be nurtured in order to improve QRM implementation and effectiveness?

9. In your opinion, what is the one (or most) key thing that must exist at a company in order for QRM to be effectively applied?

10. Is there anything else you’d like to say with regard to QRM effectiveness and maturity?

Interview candidates included a total of eleven QRM experts from industry as well as one regulator, from the HPRA. Industry experts were identified via self-identification to the researcher following the industry benchmarking survey and through active solicitation by the researcher based on the experts’ reputations and industry contributions. In each case, the interviewee was required to meet inclusion criteria consisting of the following:

- Ten or more years working in the pharmaceutical, biopharmaceutical, or medical device industries
- Five or more years working directly (or indirectly but intensively) in the QRM field

Conformance to these criteria was confirmed by a review of each interviewee’s curriculum vitae.

The interviews took place either in person or via teleconference and, with the interviewee’s consent were recorded and transcribed. In some instances, due to scheduling and geographical challenges, interviewees provided written responses directly to the researcher. The transcripts (and written responses) were then analyzed.
using a key-word identification process\textsuperscript{31} to identify emergent themes from the interviewees.

The literature review and philosophical dialogues included in the Phase 3 research followed the same structure, with the same inclusion criteria, as outlined in section 3.5.2. The learnings from the qualitative research methods were used to define QRM maturity, described in Chapters Seven through Nine of this thesis.

This ideal state, and the learnings from all three phases of the research, were then combined into a QRM maturity measurement tool. The tool was piloted with two volunteer organizations, both of whom requested to remain anonymous for this thesis. The measurement tool design, application, and feedback from the pilot case studies are discussed in Chapter Ten.

\textsuperscript{31} In some cases, synonyms were identified as key words. This was deemed necessary due to the wide variety of metaphor and “catch phrases” used in QRM expert circles, as each interviewee possessed his or her own individual “brand.” Refer to Chapter Seven for additional discussion on QRM vernacular.
Section Two: Characterizing the Current State
“Go to the people. Learn from them. Live with them. Start with what they know.”

- Lao Tzu

“Lay a firm foundation with the bricks that others throw at you.”

- David Brinkley
Chapter Four: Have Patients Realized the Benefits of QRM?

This chapter describes the research outputs and findings from Phase 1 of the research. This phase employed an explanatory sequential mixed methods approach as described in Chapter 3, beginning with quantitative methods of inquiry, then moving to a qualitative approach prior to interpretation of the results. The objective of Phase 1 was to fully characterize the current state of the pharmaceutical and biopharmaceutical industries with regard to the realization of the benefits of QRM implementation as described in ICH Q9.32

ICH Q9 discloses a number of potential benefits that may arise from the implementation of QRM principles and practices, including:

- Better assurance of product quality through proactive identification and mitigation of potential risks
- Improved compliance by enabling an understanding of the relationship between regulatory requirements and the unique concerns of the product or process
- More informed and consistent decisions relative to product quality (for realized/reactive risks) and quality system process design
- Potential reduction in the level or frequency of regulatory oversight through improved communication and higher confidence in quality system effectiveness

This phase of the research focused on the patient experience—that is, whether product quality and the resultant level of patient protection has improved since the inception of

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32 This research summarized in this section has been previously published in the *Journal of Validation Technology* (146) and presented at an industry conference (142).
ICH Q9. Based on this espoused advantage and the availability of concrete quantitative data through which to measure its realization, a quantitative study was designed.

4.1 Tangible benefits to the patient – research design and process

The Phase 1 research sought to provide a systematic review of US and Irish product recalls spanning the 2006 through 2013 time period. This timeframe was selected based on the potential to identify trends in product quality following the publication of ICH Q9 in 2005, through the most current period in which a comparable data set (i.e. a complete year of data) was available. As depicted in the literature map in Figure 4-A, this research phase extends the initial literature review described in Chapter Two.

Figure 4-A: Literature map highlighting focus for Chapter Four

Data from the US was sourced from the weekly enforcement report database available through the Food and Drug Administration website. (77) Drug recall data was reviewed in an effort to characterize product quality, and by extension patient safety, over time.
In the US, drug recalls are divided as individual events, each assigned a unique recall tracking number and associated classification level based on risk to patient or consumer. While most recalls are separated based on product presentation and dosage form, in certain instances (e.g. where all products manufactured by one firm in a given time period were subject to recall) a single tracking number was assigned to a portfolio of products. The data reviewed and presented in this section retains the separation and classification as assigned by FDA, including subsequent corrections for previously-reported data (e.g. expansion of recalled lots).

Data from the EU proved more difficult to retrieve. As a result, the research focused on Irish recall data ascertained through publicly-available annual reports written by the HPRA as well as research assistance for this project provided directly by the HPRA. As the world’s largest drug exporter and the hub of DIT, Ireland served as an obvious choice for a European perspective. To enable the identification of themes, data was coded according to a number of categories as reflected in the findings and analyzed to visualize potential trends and enable comparison between countries.

4.2 Is the patient better protected? - research findings

As noted above, one of the potential benefits of QRM is improved product quality and resultant patient safety. One indicator of patterns in this area is the number of recalls that may result from inadequate quality products reaching the marketplace. Improvements in product quality, such as the ability to meet specifications prior to drug product release, should therefore manifest as a reducing trend in the number of recall events over time. Figure 4-B and Figure 4-C depict the number of quality-related recall
events initiated from 2006 through 2013 in the US and Irish markets, respectively. (77) (78)

A review of these data reveals an increasing trend. Further analysis of US data reveals that in peak recall years (2009 and 2011), seemingly isolated issues resulted in multiple
recall events. For example, *Penicillium spp.* cross-contamination at a single firm (Aidapak Services) led to 1,021 recall events in November 2011 while cGMP deviations in June and July 2009 led to 1,107 recall events from another manufacturer (Advantage Dose LLC). While variables such as improved detection of quality defects or increases in volume of drug products on the US and Irish markets cannot be ruled out as contributing factors for the trends seen, the data indicated that recall events were increasingly common over the period in question.

This led the researcher to examine how the application of QRM may have influenced these outcomes. Table 4-1 lists the top three categories of recall events for each year included in the research. (77) (78)

Annex II of ICH Q9 highlights potential applications of QRM that, when employed appropriately, could be used to avoid these types of recalls. For example, *OOS release specification* events might have been prevented through the application of QRM “…to establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing)” and “to decrease variability of quality attributes [to] reduce product and material defects [and to] reduce manufacturing defects.” (45)
<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Contribution Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(percentage of total quality-related recall events in noted calendar year)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2013</td>
<td>US</td>
<td>Lack of sterility assurance / sterility failure (49.8%)</td>
</tr>
<tr>
<td></td>
<td>Ireland</td>
<td>Lack of sterility assurance (19.8%)</td>
</tr>
<tr>
<td>2012</td>
<td>US</td>
<td>Lack of sterility assurance / sterility failure (29.5%)</td>
</tr>
<tr>
<td></td>
<td>Ireland</td>
<td>Contamination issue (29.2%)</td>
</tr>
<tr>
<td>2011</td>
<td>US</td>
<td>Cross contamination (47.9%)</td>
</tr>
<tr>
<td></td>
<td>Ireland</td>
<td>Cold chain failure (33.0%)</td>
</tr>
<tr>
<td>2010</td>
<td>US</td>
<td>Cold chain failure (25.8%)</td>
</tr>
<tr>
<td></td>
<td>Ireland</td>
<td>Packaging or labeling issue (41.0%)</td>
</tr>
<tr>
<td>2009</td>
<td>US</td>
<td>cGMP deviations (84.9%)</td>
</tr>
<tr>
<td></td>
<td>Ireland</td>
<td>Packaging or labeling issue (42.2%)</td>
</tr>
<tr>
<td>2008</td>
<td>US</td>
<td>cGMP deviations (50.6%)</td>
</tr>
<tr>
<td></td>
<td>Ireland</td>
<td>Packaging or labeling issue (70.6%)</td>
</tr>
<tr>
<td>2007</td>
<td>US</td>
<td>Incorrect or inadequate labeling (57.2%)</td>
</tr>
<tr>
<td></td>
<td>Ireland</td>
<td>Packaging or labeling issue (27.6%)</td>
</tr>
<tr>
<td>2006</td>
<td>US</td>
<td>Incorrect or inadequate labeling (59.9%)</td>
</tr>
<tr>
<td></td>
<td>Ireland</td>
<td>Packaging or labeling issue (35.9%)</td>
</tr>
</tbody>
</table>

\(^{33}\) "cGMP deviations" is a classification for recall events given by FDA. Information regarding the impact of such deviations, or the specific nature of the deviation, was not readily available from the Agency.
Similarly, QRM could have minimized instances of *cross contamination*, *lack of sterility assurance / sterility failure*, and *microbial contamination of non-sterile products* if used “…to determine appropriate zones when designing buildings and facilities, e.g… [to] minimize contamination, prevent mix-ups, and [to determine the need for] dedicated or segregated facilities / equipment” (45)

Though it is not clear whether QRM was ineffective or simply not used in the context of these recall events, the data demonstrated that potential patient exposure to defective product has not improved since the inception of ICH Q9.
5 Chapter Five: How Mature is Industry in its QRM Application?

The Phase 1 research concluded that the patient has not yet benefited from QRM in the form of higher quality and safer medicinal products. Phase 2 of the research, as captured in this chapter, sought to characterize the correlation between QRM and this lack of benefit realization through an evaluation of the ways in which industry is currently applying QRM principles and practices to drug manufacturing. The Phase 2 research employs a variety of research methods, described in later sections, and continues the literature review introduced in Chapter Two, as shown in Figure 5-A.
This chapter explores the extent and effectiveness of QRM application in the pharmaceutical and biopharmaceutical industries. The concept of maturity was first introduced into the realm of QRM through PDA Technical Report Number 54, *Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations*, published in 2012. This report introduced industry to a simple maturity model, depicted in Figure 5-B. The PDA QRM maturity model includes five stages, stemming from no quality risk management at the lowest level through fully integrated quality risk management at the highest level. PDA positioned the model as one of the progression of *process maturity*, thereby using the conduct of QRM activities as the measure of program maturity.

In the researcher’s experience, the model reflects the general progression of a company as QRM becomes increasingly embedded within the quality system. The initial stage is a lack of QRM, in which there is no codified QRM program and risk-based assessments are not employed. This stage advances to one of *informal QRM*, where risk assessments or risk-based decisions are employed, however there is an overall lack of consistency associated with its implementation. Once a formal QRM program has taken hold, the third level of maturity is reached, where risk activities are generally *reactive* in nature, addressing issues that have already occurred in order to understand the impact of the event. As companies focus more on anticipation and avoidance of risks through *proactive* risk identification, assessment, and control, QRM programs evolve into a more established, prospective state. Finally, the most mature level is reached, where QRM principles and practices are woven into the fabric of the quality system and product lifecycle and are therefore transformed into the normal operation of the business, as shown in Figure 5-B. (62)
The PDA Technical Report provides a second example of a risk maturity model, adapted from a model originally proposed under the umbrella of supply chain risk management. This alternative model explores some of the cultural factors that support and act within a QRM program, as shown in Table 5-1. (62)

Table 5-1: Alternative risk management maturity model presented in PDA Technical Report No. 54

<table>
<thead>
<tr>
<th>Risk Maturity Level</th>
<th>Risk Processes</th>
<th>Attitude</th>
<th>Behavior</th>
<th>Skills &amp; Knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skepticism</td>
<td>No formal processes</td>
<td>Accidents will happen</td>
<td>Fear of blame culture</td>
<td>Unconscious incompetence</td>
</tr>
<tr>
<td>Awareness</td>
<td>Ad hoc use of stand-alone processes</td>
<td>Suspended belief</td>
<td>Reactive, fire fighting</td>
<td>Conscious incompetence</td>
</tr>
<tr>
<td>Understanding &amp; Application</td>
<td>Tick box approach</td>
<td>Passive acceptance</td>
<td>Compliance, reliance on registers</td>
<td>Conscious competence</td>
</tr>
<tr>
<td>Embedding &amp; Integration</td>
<td>Risk management embedded in business</td>
<td>Active engagement</td>
<td>Risk-based decision making</td>
<td>Unconscious competence</td>
</tr>
<tr>
<td>Robust Risk Management</td>
<td>Regular review &amp; improvement</td>
<td>Champion</td>
<td>Innovation, confident &amp; appropriate risk management</td>
<td>Expert</td>
</tr>
</tbody>
</table>
The second model offers general concepts for each maturity level within four different dimensions—risk processes, attitude, behavior, and skills and knowledge. No additional information, such as the distinction between concepts or how to progress from one level to the next, is offered. In the absence of a fully formed QRM maturity model (the gap this research intends to fill), the two example risk maturity models from PDA Technical Report No. 54 were used as the frame of reference to measure the current state of industry with regard to QRM. Though QRM maturity is likely to be a continuum rather than one marked by discrete tiers, for clarity of analysis the researcher chose to employ five levels of maturity, as shown in Figure 5-C.

![Figure 5-C: Basic QRM maturity model used for Phase 2 research](image)

### 5.1 Has industry improved the level of compliance since the publication of ICH Q9?

#### 5.1.1 Research design and process

The Phase 2 research began with a systematic review of US and Irish compliance enforcement data spanning the 2006 through 2013 time period. Similar to Phase 1, this timeframe was selected based on the potential to identify trends in cGMP compliance
following the publication of ICH Q9 in 2005, through the most current period in which a comparable data set (i.e. a complete year of data) was available.

US data was collected from the warning letter database available through the FDA website. (81) Warning letters issued by FDA for cGMP-related concerns were selected based on the insight they may provide into the industry’s state of compliance over time. FDA is charged with protecting public health and as such has several levels of compliance enforcement options available to facilitate this mandate. (82) Compliance observations noted during inspections are summarized on a Form 483. Unlike the practice in the EU, these observations are not categorized according to criticality and therefore may not delineate the gravity of noncompliance concerns as identified during inspections; in addition, access to individual Form 483s are not readily available. Warning letters represent the “principal means of achieving prompt voluntary compliance” with applicable regulations and are typically issued for significant violations of related statutes or, in many cases, inadequate responses or commitments from violative firms following the issuance of a Form 483. (83) Warning letters are posted to a public access database and have the potential to offer a rich source of information regarding noncompliance with cGMPs. Various cross checks (i.e. database searches by year, company name, warning letter category, product type, and keywords) were performed to assure the validity and comprehensiveness of the data collected.

Inspectional observations in the EU are not readily available to the public; the researcher therefore relied on assistance provided directly by the HPRA and therefore focused solely on the scope of inspections from the Irish authorities. (78) (79) To enable the identification of themes, data was coded according to a number of categories and analyzed to identify patterns.
5.1.2 Research findings

Another potential benefit of QRM implementation described in ICH Q9 is reduced regulatory oversight, which may be achieved through demonstration of quality system effectiveness in the form of a robust QRM program. (45) (52) This allows trust to be built between regulators and manufacturing sites, as regulators have visibility to the depth of product and process knowledge at a site, as well as their level of self-awareness over their own quality vulnerabilities. It stands to reason that, where firms fully embrace the principles and practices of QRM, incidences of breaches of cGMP, product quality defects, and resultant risks to the patient should reduce and compliance status should improve over time. This should allow manufacturers to demonstrate the enhanced effectiveness of their pharmaceutical quality systems through the use of meaningful quality metrics, such as reductions in the number of deviations, effectiveness of CAPAs and change requests, and a reduction in the number customer complaints.

Figure 5-D illustrates the overall number of cGMP-related warning letters issued by FDA from 2006 through 2013. (81) The increased numbers of compliance enforcement actions since 2006 indicated that cGMP compliance, and therefore quality system effectiveness, had not improved since the inception of ICH Q9.
The researcher acknowledges that further analysis of variables, such as the total number of cGMP inspections conducted in each calendar year and the proportion of inspection observations (Form 483s) that ultimately resulted in warning letters, would allow for a refined interpretation of the data; however, such information is not readily available from FDA.

A review of warning letters through the lens of QRM revealed an increasing trend of citations against the QRM programs and practices themselves, as shown in Figure 5-E. This would indicate that, in the opinion of the inspectors, many applications of QRM had not inspired confidence that the manufacturing site has appropriately interpreted contemporary guidance and regulations within the context of their individual operations.
Again, while additional variables such as increased QRM education of inspectors or an evolving strategic emphasis on QRM may be at play, insight into the nature and extent of impact of such variables is not available. Nonetheless, these data confirmed a gap between regulatory expectations and industry practice over the period reviewed. This conclusion was reinforced with additional analysis into the various categories of QRM citations. Figure 5-F illustrates whether each individual citation indicated either an absence (i.e. failure to apply QRM where warranted based on an individual event or circumstance) or misapplication (i.e. inappropriate use of QRM principles or faulty conclusions drawn based on QRM application). For example:

- Absent QRM: “…we note that your response includes a commitment to retrain personnel, revise procedures, and use of premade agar plates to address
[deficiencies in aseptic processing techniques]. Your response is inadequate because your firm failed to conduct a comprehensive risk assessment of these poor aseptic process activities, and the inadequate environmental monitoring program, to evaluate their impact on product quality.” (84)

- Misapplied QRM: “We are concerned…with your risk assessment, which suggests that the failure of these products to meet acceptance criteria for defects during the 100% inspection has no bearing on the quality of the released units. Please provide detailed information regarding how you reached your conclusion.” (85)

An absence of QRM was cited in the overwhelming majority of instances. This was striking, considering that ICH Q9 had been published many years prior; it would be reasonable to expect that sufficient time had elapsed to allow industry to overcome some of the initial inertia inherent in any paradigm shift, even one of the magnitude of transitioning from “rule-based” to “risk-based” quality and compliance.
Analysis with respect to the QRM lifecycle stage that was cited in the warning letter was similarly informative. Figure 5-G shows the proportion of citations for the various sections of the lifecycle: risk assessment, risk control, risk review, risk communication, or risk management as a whole.

![Figure 5-G: Quality Risk Management Deficiency by Lifecycle Stage in US FDA Warning Letters Issued between 2006 and 2013](image)

The majority of citations implicated risk assessment, the first phase of the QRM lifecycle. Because QRM is an iterative process that commences with a robust and science-based risk assessment, citations in this area of the lifecycle were particularly concerning since it is unlikely that the remaining phases would prove effective if built upon a faulty or absent risk assessment. The data is also revealing as to the level of risk maturity of implicated firms—observations related to the risk review portion of the QRM lifecycle were notably absent. Perhaps this is because practitioners failed to successfully complete the risk assessment and risk control portions of the lifecycle; if
so, it is likely that risk review phase was not reached. Unfortunately, it appears that risk review has been neglected for some time, as a 2006 PDA survey on QRM practices noted that a large proportion (41%) of respondents did not periodically reassess risk assessments, while the majority (55%) did not evaluate the QRM program for effectiveness. (86)

These data support the hypothesis that certain firms within industry are still in the early phases of QRM maturity (i.e. Level 1 “no quality risk management” or Level 2 “informal quality risk management”, based on the model depicted in Figure 5-C), with challenges centered on the initial risk assessment phase of the QRM lifecycle.

Another indicator as to the expected level of QRM maturity is whether warning letter citations focus on reactive or prospective QRM implementation. While it is broadly acknowledged that risk management applied in response to a realized issue (i.e. reactive) can be helpful to get to true root cause and plan and to define an appropriate remediation strategy, most risk management practitioners will assert that the full value of QRM is achieved through proactive anticipation and mitigation of potential risks to ensure those issues do not materialize. (45) (62) When QRM-related warning letter citations were classified by emphasis (i.e. prospective or reactive; Figure 5-H), it was evident that industry shortcomings were primarily focused on reactive QRM during the prior eight-year period.
Examples of this emphasis are evident in the following excerpts:

- “Please provide a copy of your investigation [surrounding breach of data integrity through the deletion of critical analytical data and backdating records], along with your risk assessment regarding the extent and impact of the missing data on the quality of all finished drug products released for distribution.” (87)
- “…your firm failed to investigate numerous customer complaints for several lots of [product] concerning cracked vials… your firm's response failed to include a risk assessment for the product currently on the market.” (88)
- “…your firm failed to conduct and document verification under actual conditions of use of [multiple] laboratory test methods… [in your response] please provide a risk assessment for possible impurities present in [lots of API released to market].” (89)

In these instances FDA was calling for the application of QRM in situations where an impact assessment might have been used traditionally, i.e. where the full breadth and
gravity of a cGMP-related event or circumstance must be determined. This trend implied that FDA expected industry to have mastered reactive/corrective QRM, or be positioned at a Level 3 on the QRM maturity continuum. Therefore, a gap between the risk maturity status of industry (Level 1 or 2) and FDA expectations (Level 3) was apparent.

While a comparable data set was not available from Ireland, excerpts from HPRA inspectional observations indicated a similar gap in QRM maturity. For example:

- “With regard to the usage of the flexible isolator / barrier for the dispensing of [material X] in [room Y], there was no formal risk assessment documented assessing the impact of the introduction of the flexible isolator on pre-existing activities in the room.” (emphasis proactive, risk assessment; (79))
- “Following a risk assessment exercise that had been performed in 2011 on the use of diaphragm pumps at the site following a diaphragm pump failure issue that had occurred at a sister site, appropriate actions had not been taken to ensure that the controls on which the risk had been deemed acceptable in (Site) were effective…” (emphasis proactive, risk control; (79))

These findings indicate that (as of 2013) the pharmaceutical and biopharmaceutical industries were still struggling with QRM. Maturity levels in QRM application were low, and the benefits suggested in ICH Q9 had not yet been realized.

5.2 How is QRM currently being applied throughout industry?

In addition to the use of compliance enforcement data as a means to characterize the level of risk maturity, the researcher sought data and opinion directly from industry through the design, deployment, and analysis of an industry benchmarking survey.
5.2.1 Research design and process

The design of the industry benchmarking survey began by outlining the knowledge to be gained, such that the survey questions would align with the goals of the research. The researcher sought to explore three pillars that compose QRM—people, process, and governance—that in turn support the patient, as depicted in Figure 5-I:

![Figure 5-I: Pillars of a QRM program](image)

Because programs such as QRM require the engagement and dedication of practitioners to work within it, people was selected as the first pillar to explore. This line of inquiry focused on understanding the motivations, behaviors, and attitudes towards risk management of the personnel who support and execute the QRM program. Processes were investigated in order to measure where and how QRM is applied, using Annex II.
of ICH Q9\textsuperscript{34} and the contents of PDA Technical Report No. 54 as guides. Finally, questions related to governance, such as the support from leadership, ownership, and accountability, were included.

The survey was structured to elicit feedback from respondents regarding the percent of time spent on a particular QRM activity, the percent of colleagues who might express certain opinions, and how various QRM activities had been codified within the umbrella quality system. In this way, the survey served as a \textit{quantitative} research method, enabling extensive analysis and trending of resultant data.

The first two questions of the survey addressed inclusion criteria for the research subjects. The survey began with a research brief, developed as part of the documentation package for the Research Ethics Committee, including contact information for the researcher. The brief was followed by a mandatory question regarding consent—respondents who indicated that they did not consent to participation in the research were directed to a “thank you” page and not permitted to continue with the survey. Respondents who granted consent through this initial screen were allowed to continue to the next mandatory question regarding their current employment status. Respondents who self-identified as consultants were likewise directed to the “thank you” page and not permitted to complete the remainder of the survey. This ensured that respondents answered based on their current experience with their current employer (either a Marketing Authorization Holder (MAH), Contract Manufacturing

\textsuperscript{34} As discussed in Chapter Two, Annex II of ICH Q9 lists potential applications of QRM throughout the quality system. Different quality system elements, such as product development, validation, deviation management, change control, and sampling are listed, along with the objectives of using QRM in each context. The content of this Annex was captured in the benchmarking survey to measure where and to what extent integration may have occurred at a given company.
Organization (CMO)/Contract Research Organization (CRO), or other type of company), rather than based on a portfolio of companies they might support, and therefore assured fidelity of responses based on the targeted research objectives.

Following these inclusion questions, general demographic information (including product types, company size, company location, applicable product lifecycle phases, respondent’s functional group, and respondent’s position within the company) were asked to enable subsequent analysis. The survey continued with general questions regarding the existence of a QRM procedure or policy, compliance with ICH Q9, and inspection status and results. The remaining questions were considered optional (to reduce the risk of respondent fatigue and cessation of participation) and focused more specifically on the elements of people, process, and governance described above.

The survey, once drafted, was reviewed by the researcher to ensure questions were clear and unambiguous, and that the question design would support the research objective. The survey was then reviewed by third parties (other members of the PRST) to provide additional feedback prior to coding in the SurveyMonkey software application. Once coded by the researcher, the electronic survey was piloted by PDA personnel to confirm the integrity of the flow associated with the inclusion criteria. All pilot responses were deleted, and a link to the survey was provided via email to applicable PDA members and published in the *PDA Letter*, which also announced the research collaboration effort.

The survey was opened on October 1, 2015 and remained active through December 31, 2015. Shortly thereafter, the leader of the QRM workstream from PDA Japan requested that the researcher reopen the survey to allow for additional responses from members
in that PDA chapter. The researcher obliged, and the survey finally closed on January 31, 2016.

Responses to the survey were downloaded from SurveyMonkey, encrypted as described in section 3.2, and analyzed. A general analysis of industry as a whole was conducted, using all responses to the survey. In addition, three sub-analyses were performed in an effort to identify any new perspectives that might be revealed: analysis by region (based on the location of company headquarters, using the primary ICH regions of EU, US, and Japan), analysis by company size (based on number of employees), and analysis by respondent position within their company (i.e. executive management, senior management, middle management, supervisory level, and individual contributor level). Initial findings from the QRM benchmarking survey were shared at the PDA Annual Meeting in March 2016, followed another talk at the PDA Japan Annual Meeting in November 2016.

### 5.2.2 Research findings

Two hundred and thirty industry practitioners accepted the invitation to complete the QRM benchmarking survey, with approximately 144 of these providing complete responses. Though not statistically significant in a strict sense, this response rate enabled a vigorous analysis that could provide insight into the general level of QRM maturity within the pharmaceutical and biopharmaceutical industries. The

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35 According the 2012 US census, over 810,000 people work in biopharmaceuticals in the US alone. Even within this small cross-section of industry, a statistically significant sample size would require 384 responses, given a 95% confidence level and a +/- 5 confidence interval.
demographic information provided by respondents indicated a broad variety of industry sectors were represented.

As shown in Figure 5-J, eighty percent of respondents were employed by MAHs, with eleven percent working for CMOs. The remainder worked for companies that perform both functions, or fall into other categories, such as contract testing laboratories.

A variety of company sizes were also represented, with the greatest response rate representing medium- and medium/large-sized companies, as shown in Figure 5-K.

Respondents represented companies headquartered throughout the world, the majority of which were based in the ICH regions of EU, US, and Japan, as shown in Figure 5-L. In addition, half of respondents were physically located in the US (50%), followed by Japan (22%) and Europe (14%).
For the purposes of this survey, small companies were defined as those employing less than 500 people; small/medium companies employed between 500 and 1,000 people; medium companies had between 1,001 and 5,000 people; medium/large companies between 5,001 and 10,000 people, large companies between 10,001 and 50,000 people, and very large companies employing more than 50,000 people. These intervals were selected to represent company size based on the potential correlation with the number of (human) resources available to work within a QRM program.
Questions surrounding the respondents’ roles at their firms revealed a nearly even split between those working at a site versus those working at the corporate level (54% and 46%, respectively). These data may reveal some limitations associated the survey, since, depending on the company, respondents working at the corporate level (across multiple sites) may have only indirect knowledge regarding the actual practices and attitudes towards QRM at the site level. Some inconsistencies in the data, based on direct versus indirect knowledge, are therefore possible.

Respondents also cover a broad swath of positions within the company, with middle management-level roles providing the largest proportion of responses (Figure 5-M). Furthermore, nearly two-thirds of respondents work in the quality assurance or quality systems fields, heavily weighting data trends towards the knowledge and perspective of the quality unit, at the expense of operations (Figure 5-N).

Figure 5-M: Demographics – Respondents’ position
With regard to product type, dosage form, and product lifecycle phase, biologics and sterile injectables received the highest representation, as did the commercial phase of the product lifecycle, as shown in Figure 5-O through Figure 5-Q. Given the primary source of volunteers for the survey (i.e. members of the PDA), these demographics are not surprising. Indeed, the majority of the respondent pool works within what is commonly considered to be the most complex product types (biologics), that reach the most people (commercial phase of product lifecycle) as well as those that carry the most risk to patient (sterile injectables). It is reasonable to expect that given the climate in which these respondents operate, particular attention would be paid to identifying and managing risk.
Figure 5-O: Demographics – Product type(s) manufactured by respondents’ companies

Figure 5-P: Demographics – Dosage form(s) manufactured by respondents’ companies
A full 90% of respondents indicated that their company has a QRM policy or procedure in place to document how QRM activities are performed. Five percent of respondents indicated that their company does not have such a document in place—this is alarming, particularly since the respondents work for firms within the ICH countries of US and Japan, for which ICH Q9 has a decade-long tenure. An additional 5% of respondents were not sure of whether their company has such a document. Nonetheless, there has been significant progress in this area since 2006, when only 48% of companies had implemented QRM with an additional 30% citing their efforts as “in progress.” (86) Nearly all of the respondents who indicated negative or uncertain responses to this question in the benchmarking survey did not continue with the remainder of the survey.

The majority of respondents indicated that their companies’ QRM programs had been inspected by regulatory authorities, as indicated in Figure 5-R. In the experience of the respondents, the US FDA and European National Competent Authorities (indicated as “EU”) review QRM programs in more than half of their inspections. The responses
suggest that Japanese PMDA and Australian TGA do not appear to review QRM as often. Health Canada (included in the “Other” category) also seems to have taken an interest in firms’ QRM programs, although to a lesser extent than its southerly neighbor.

![QRM Inspection Status](image)

**Figure 5-R: Compliance – QRM program inspection status**

When asked about the outcomes of these inspections, the majority of respondents (53%) indicated that their QRM programs only partially meet regulatory expectations (Figure 5-S). This is quite curious, considering that 86% of respondents indicated that their firms’ QRM programs were compliant with ICH Q9. These data provide additional evidence of a gap between regulators’ expectations of industry and actual industry practices; a gap identified by the researcher during the data analysis of quality defects and compliance observations discussed in section 5.1. This discrepancy may be due to incomplete knowledge on behalf of the respondents, or differences between the ICH Q9 source documents and regulators’ understanding of how the guidance should be implemented within the overarching quality system.
People: The first pillar of QRM

Respondents then completed a series of questions regarding attitudes and opinions—the *people* element of the survey. A statement was proposed, and respondents were asked to estimate the percent of their colleagues who might agree with the statements. Statements expressed both *positive* (i.e. in favor of QRM) and *negative* (i.e. opposed to QRM) opinions, which were then coded and graphed during the analysis to illustrate a potential risk maturity level. This analysis was conducted such that the more people agree with a positive opinion and disagree with a negative opinion, the higher maturity level.

The first question sought to explore the general level of QRM awareness at respondents’ firms through the question “[What percent of your colleagues…] have no knowledge
of QRM principles or practices?” This represented a negative opinion, so the results were graphed to show that the fewer people lacked knowledge, the more mature that firm might be. As seen in Figure 5-T, the majority of industry ranks at a Level 4 maturity with regard to QRM awareness, with an average response of 3.4. Some differences were seen when considering the data by sub-group. For example, individual contributors felt that the QRM knowledge of their colleagues was closer to a Level 3 (average of 3.2), while more senior managers estimated this at closer to a Level 4 (average of 3.6). Similarly, awareness of QRM principles and practices appear to be much stronger in companies based in EU (average of 3.9) than those in the US and Japan (averages of 3.3 in both regions).

Looking past mere awareness into the amount of support offered by industry personnel, respondents were asked “[What percent of your colleagues...] resist participating in
QRM-related activities?” As a negative behavior, the results were graphed to show that the more people exhibit this tendency, the less mature the company with regard to QRM. As seen in Figure 5-U, the majority of industry scored a Level 4, with an average response of 3.8. Similarly, differences were seen in responses by sub-group, with small and smaller/medium companies indicating a higher level of support for the QRM program (averages of 4.0 and 4.3, respectively) than large and very large companies (with averages of 3.6 and 3.7). In the ICH regions, Japan exhibited the lowest level of support (average of 3.6), followed by the US (3.8 on average) and the EU (4.0 on average).

![Figure 5-U: People – Level of support for QRM](chart.png)

With respect to the people pillar of QRM, maturity began to wane with the level of engagement within the program. When asked “[What percent of colleagues…] are eager to learn and participate in QRM-related activities?” respondents indicated that...
industry sits at a Level 3, responding with an average of 3.2 (Figure 5-V). This response was relatively consistent across sub-groups, with no significant differences in maturity seen based on company size, respondent position, or region.

A similar drop in maturity was seen when respondents were questioned about their colleagues’ advocacy for QRM, with the majority of industry seated at a Level 2 and an average response of 2.8 (Figure 5-W). In addition, companies based on the EU appear to have stronger advocates for the program (an average of 3.2) than do Japan and the US (averages of 2.9 and 2.8, respectively).
The *people* elements described above (awareness, support, engagement, and advocacy) can be placed on the QRM maturity continuum, since each attitude and behavior is a precursor to those that follow. For the purposes of gauging QRM maturity with regard to the people working within it, the highest level (Level 5) was defined as a state where QRM no longer requires deliberate advocacy, since the principles and practices have become such a part of daily operations that QRM is seamless with other aspects of manufacturing and the quality system. Through this lens, the pharmaceutical and biopharmaceutical industries score a Level 3 (average = 3.3)—that is, a state in which people are aware of QRM tenants and practices at their firm, are supportive of the program, and are engaged in applying the program to their own work (Figure 5-X). Industry has not yet achieved the ranks of actively championing the program, which may play in role in the level of maturity seen for the other two pillars of QRM: *process* and *governance*.
Figure 5-X: Industry’s current level of maturity with respect to the people interacting with the QRM program

**Process: The second pillar of QRM**

The survey then transitioned into a series of questions aimed at characterizing industry’s level of maturity from the perspective of the *process*. The first of such questions sought to explore the extent to which industry has integrated QRM into other aspects of the quality system. The majority of the quality system elements embedded within this category were taken directly from Annex II of ICH Q9; therefore this question provided insight into the extent of compliance and potential gaps between industry’s current state and regulator expectations that were identified earlier in the research. For a series of quality system applications, respondents were asked whether QRM was applied consistently (as a procedural requirement), ad hoc (not a procedural requirement but applied on occasion), or not at all. Currently, the majority of industry applies QRM consistently in ten of the seventeen elements: deviations, CAPA, change control, complaints and quality defects, product and process characterization, product and process development, systems lifecycle management, environmental monitoring, internal audit, and supplier management, as shown in Figure 5-Y.
Figure 5-Y: Process – Level of integration of QRM principles and practices into the quality system.
These results are disappointing, given the direction offered in ICH Q9 and the potential benefits available were QRM applied to the other twelve quality system elements. That said, differences seen on a regional basis indicate that some companies have embraced these uses, with European-based companies showing a much stronger level of integration than US or Japan (Table 5-2). In addition, as might be expected based on the availability of resources, larger companies tended to have a higher level of integration than smaller companies.

Table 5-2: Matrix of quality system elements where QRM is consistently applied by ≥50% of respondents, by region

<table>
<thead>
<tr>
<th>Quality System Element</th>
<th>ICH Region</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Europe</td>
<td>US</td>
<td>Japan</td>
</tr>
<tr>
<td>Deviations</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CAPA</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Change control</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Complaints/quality defects</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Product/process characterization</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Product/process development</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Systems lifecycle</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplier management</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Environmental monitoring</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Technology transfer</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process validation lifecycle</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal audit</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cleaning</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage and distribution</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packaging and labeling</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMO management</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The process pillar of QRM is associated not only with where in the quality system QRM is applied, but also how it is applied. To that end, the next set of questions focused on characterizing the extent to which QRM is structured in its application. The structure of QRM should not be confused with the level of formality applied to the QRM process; formality refers to the rigor associated
with QRM application (typically risk assessment), whereas structure refers to how well the QRM process is defined. Even less-formal applications of QRM should be well-defined, to enable consistency of application and ensure conclusions are commensurate with the assessment performed; as such, more mature QRM programs should tend to be well structured in their application. The responses to these questions were curious, as one might expect that QRM is applied in either a well-defined or loosely-defined way. However, as shown in Figure 5-Z and Figure 5-AA, the majority of industry uses well-defined QRM methodology <25% of the time, and also uses loosely-defined QRM methods <25% of the time, with responses averaging a 3.4 in maturity for unstructured application and 2.9 for well-structured application. While smaller companies tend to apply QRM more often in a loosely-defined way than do larger companies, the difference was nominal and did not extend to other sub-groups such as region or position.

![Figure 5-Z: Process - Percent of time QRM is applied in a well-defined way](image-url)
The next set of questions endeavored to determine when QRM was most often applied: either reactively, in response to a risk that has been realized or event that has occurred, or proactively, to identify and manage risks before they are realized. While it is important to strike a balance between the two, risk principles and practices yield the greatest advantages when applied in a proactive setting, to identify preventive actions that enable the anticipation and avoidance of risks to product quality and patient safety. Despite the broad acknowledgement of this fact from regulators, experts, and practitioners alike, it appears that the pharmaceutical and biopharmaceutical industries have not yet harnessed the proactive application of QRM. Figure 5-BB and Figure 5-CC indicate that the majority of industry is in transition, performing risk management before and after events in equal measure.
**Proactive:**
"How would you estimate the percent of time your company spends applying QRM proactively / prospectively?"

![Proactive Chart]

**Reactive:**
"How would you estimate the percent of time your company spends applying QRM reactively / retrospectively?"

![Reactive Chart]

Figure 5-BB: Process – Percent of time QRM is applied proactively

Figure 5-CC: Process – Percent of time QRM is applied reactively
The final inquiry relative to the *process* pillar of QRM strove to characterize the perspective with which QRM is applied; specifically, whether QRM is applied in a targeted manner (e.g. looking a single risk such as cross-contamination across a number of products or systems) or a holistic manner (e.g. exploring all potential risks associated with a given process or products). While there are advantages and limitations associated with each approach, it is likely that a balance of the two would best enable a vertically integrated risk portfolio. Figure 5-DD and Figure 5-EE demonstrate that the majority of industry is focused on assessing and managing previously identified risks (such as the cross-contamination example used above), rather than employing a more all-inclusive approach to risk identification and control. The exception appears to be companies in the EU, where respondents indicated that holistic risk management occurs more frequently than targeted applications. While a targeted approach is beneficial to evaluate a specific harm when it emerges, an unbalanced emphasis on conducting discrete QRM efforts aimed at known risks can lead to a myopic perspective regarding the true number of risks present for a given product or process, thereby limiting the effectiveness of risk identification.
Targeted:
"For the QRM activities undertaken at your company, how would you estimate the percent of time your company spends assessing specific risks (e.g. cross contamination, data integrity, etc.) across multiple systems / processes?"

Holistic:
"For the QRM activities undertaken at your company, how would you estimate the percent of time your company spends assessing multiple types of risks within entire systems / processes / product lines (e.g. cell culture, tableting, fill/finish, Pr..."

Figure 5-DD: Process – Percent of time QRM is applied using a targeted approach

Figure 5-EE: Process – Percent of time QRM is applied using a holistic approach
From the perspective of the QRM process, responses to elements such as the level of integration, underlying structure, timing of application, and perspective of application indicate that industry is currently seated at a Level 3 (Figure 5-FF).

![Figure 5-FF: Industry’s current level of maturity with respect to the QRM process](image)

**Governance: The third pillar of QRM**

Questions exploring the *governance* pillar of QRM were structured in a similar manner to those addressing people—that is, an opinion was posited and respondents were asked to estimate the percent of their colleagues who might agree. For the purposes of the survey, governance addressed ownership and accountability for QRM, as well as the way in which QRM supports decision-making. Since these concepts are often driven by the overall QRM policy and the behaviors of senior leadership at a firm, governance may be considered “the tone at the top” from which personnel take their cue.
The first question addressing the level of maturity for governance asked “[What percent of colleagues might say that] the application of QRM is the responsibility of the Quality organization?” As shown in Figure 5-GG, the majority of industry achieved only a Level 2 on the maturity scale, with an average response of 2.5. However, some distinct variations in responses were seen within sub-groups. In Japan, for example, responses averaged 2.4, while companies in the US were closer to a Level 3 (average = 2.9). Small companies also tended to score lower relative to ownership, indicating an average of 1.9, whereas large companies averaged 3.0.

![Figure 5-GG: Governance – Ownership of QRM](image)

When asked about accountability for QRM via the question “[What percent of your colleagues might say that] QRM should be performed across all levels in the organization (shop floor to senior management)?” the majority of industry ranked a maturity Level 2, although the number of responses on the higher end of the maturity scale elevated the average response to a 3.0 (Figure
As a sub-group, companies based in Europe were slightly more mature (average = 3.3) than those in Japan or the US (averages 3.1 and 2.9, respectively).

Figure 5-HH: Governance – Accountability for QRM activities

Figure 5-II shows that industry is squarely at a maturity Level 3 with regard to an understanding of one of the primary functions of QRM—to enable risk-based decision making. When asked “[What percent of your colleagues might say that] QRM should be applied before a decision is made, to help inform the decision-making process?” respondents provided an average reply of 3.1. This was relatively consistent across sub-groups, although regional differences were seen, with European companies providing an average response of 3.6, Japanese companies a 3.3, and US companies a 2.8—the least mature of the three primary ICH regions with regards to understanding this principle of QRM.
The last survey question addressing governance asked “[What percent of your colleagues might say that] QRM can be used to justify current practices / a decision that has already been made?” This question was classified as the level of complacency within an organization, since using QRM to justify current practices, rather than to define the optimal path forward, reduces the firm’s ability to identify opportunities for improvement. As shown in Figure 5-JJ, the majority of industry scores a Level 4 in this area, however the number of responses falling below this maturity model resulted in an average response of 3.0. There were slight but meaningful differences across regions, with European companies once again being more mature than industry as a whole, with an average response of 3.2. The US measured an average of 3.0, with Japan falling behind at 2.8. Executive-level management also indicated a less mature response, averaging 2.5, which is concerning considering the influence individuals at that level exert over the direction of a firm. The responses
for this question is rather disturbing, as it implies that companies are biased towards the outcome of QRM and may be “reverse-engineering” risk assessments to support pre-determined conclusions.

![Complacency:](image)

**Figure 5-JJ: Governance – Use of QRM to justify complacency**

The elements of ownership, accountability, purpose, and complacency that compose the governance pillar of QRM entail similar concepts that can be combined into five maturity levels on the continuum. The first of these is an immature state with no governance in place—a state where leadership has not established an appropriate tone for the application of QRM. From there, a firm might reach a state with a loose governance structure, albeit one that lacks meaningful management support. The third governance maturity level is one that is fully functioning, but where success can be attributed to pockets (or siloes) within the firm. Level 4 firms would have progressed to state with broader engagement of functional groups; one where personnel apply
QRM to their own areas and are held accountable for knowledge and reduction of risks. Finally, the highest maturity level would entail a fully integrated governance structure where risks are being managed and are visible through all layers of management. Based on the responses received through the benchmarking survey, industry is currently at a Level 3; a state in which QRM has not fully penetrated the fabric of the firm and is siloed in its application (Figure 5-KK).

![Figure 5-KK: Industry’s current level of maturity for QRM governance](image)

**Questions of value**

The survey progressed to ascertain the *value* that respondents felt QRM brought to their daily operations. The first of such questions asked “[What percent of your colleagues might agree that] QRM is a box-ticking exercise with no real value?” Respondents made a clear statement that this is not the case, indicating that this was a rare sentiment throughout industry (Figure 5-LL).
Similarly, when asked whether QRM enabled product quality improvement, quality systems improvement, and business objective realization, the majority of respondents felt risk management was either valuable or very valuable (75%, 77%, and 61%, respectively, as shown in Figure 5-MM through Figure 5-OO).

![Graph showing the perception of QRM value to the organization.](image)

**Figure 5-LL: Value – Perception that QRM adds value to the organization**

![Graph showing the value of QRM for improving product quality.](image)

**Figure 5-MM: Value – Value of QRM for improving product quality**
Figure 5-NN: Value – Value of QRM for improving quality systems effectiveness

Figure 5-OO: Value – Value of QRM for enabling business objectives to be met
Based on the QRM benchmarking survey results, the current state of maturity in industry is a Level 3 for the people and process pillars of QRM, and a slightly lower 2.5 for the governance pillar. While no meaningful distinctions were found based on company size or respondent perception based on position, there is a clear difference in maturity based on region. Companies based in the EU (between Level 3 and Level 4) appear to be more mature than the US (Level 3), which in turn appears to be more mature than Japan (between Level 2 and Level 3). Correlating factors for this phenomenon include the extent to which QRM has become embedded within regional regulation, and the degree to which regional regulatory authorities inspect QRM programs.

Irrespective of region, ten years after the publication of ICH Q9, one might expect industry to be further along the path towards maturity; however, the majority of respondents felt their QRM programs were on par with other companies in industry (Figure 5-PP). Potential obstacles impeding a more mature state are explored in section 5.3.

Figure 5-PP: Benchmarking – Estimate of QRM program maturity when compared with other companies in the industry
The last question in the benchmarking survey sought to validate the research plan. Respondents were asked whether their companies had interest in benchmarking their QRM programs with other companies, to better understand best practices and pitfalls. Over half of respondents (56%) indicated that such a need exists, with another 29% being unsure. The remainder of the research effort, including the development of a QRM maturity measurement tool, aims to fill this gap for industry.

5.3 What obstacles might be preventing a more mature state?

5.3.1 Research design and process

Following the quantitative analyses performed to evaluate whether the patient has fully realized the benefits of QRM and to benchmark risk maturity throughout industry, the qualitative portion of Phase 2 began. This phase used literature review and philosophical dialogues to understand potential obstacles that have impeded industry’s path towards a more mature state. Philosophical dialogues were conducted at a series of industry conferences comprised of delegates from multiple areas of expertise; these conversations included representatives from industry, regulatory authorities, and academia. This section of the report addresses the primary themes regarding barriers to progress in QRM that were revealed during the philosophical dialogues, some of the researcher’s own experience as an “insider,” and references to the literature where applicable.
5.3.2 Research findings

**Misconceptions regarding quality vs. compliance, or “taking a conservative approach”**

The first theme that emerged from the philosophical dialogues was confusion between compliance with ICH Q9 and effectiveness of QRM implementation. These, of course, are two very different concepts; compliance is often defined as “following regulation” or applying the GMPs, while effectiveness in QRM stems from applying the regulations in a way that has tangible benefits such as product quality improvement, quality systems improvement, and realization of business objectives. In order to better gauge the perspectives of industry practitioners relative to this distinction, the researcher asked conference delegates to sketch their understanding of the relationship between quality and compliance using a Venn diagram format. Venn diagrams are graphs of interlocking circles that are often used to demonstrate the relationship between categories, including the relative size or contribution of each category (as depicted by the size of a given circle) and the level of similarities and differences between categories (as depicted by the extent to which the circles overlap). Over the course of the three years of research, the researcher had the opportunity to see dozens of Venn diagrams illustrating the perceived relationship between quality and compliance in industry; a pattern emerged early on, and has been reinforced many times at multiple industry conferences. The vast majority of delegates drew a diagram similar to that shown in Figure 5-QQ.
This implies that most of industry believes that there are aspects of quality that are unrelated to compliance, and more worryingly, that there are aspects of compliance that are unrelated to quality. With this being the paradigm under which some members of industry operate, it is not surprising that quality culture has become a topic of concern with regulators, since this opinion could embitter personnel to compliance and QRM-related activities if the value is not understood. While an excellent article was written by members of the PRST to dispel this misconception (90), the frequency with which a void between quality and compliance is cited indicates the mindset has not yet taken hold.

This poses a serious challenge to the enhancement of QRM maturity in industry, since the difference between quality and compliance (or compliance and effectiveness) is fundamental to understanding the role that QRM plays in the pharmaceutical and biopharmaceutical industries. ICH Q9 notes that “appropriate use of quality risk management can facilitate but does not obviate
industry’s obligation to comply with regulatory requirements” (45)—a tenant that (in the researcher’s opinion) should be understood to mean that QRM is a mechanism through which compliance-related activities can be linked to product quality. In addition, QRM offers industry an opportunity to define what quality looks like for their patients, products, and businesses, beyond the basic requirements associated with regulatory compliance. As a result, the Venn diagram showing the relationship between quality and compliance through the lens of QRM looks more like that shown in Figure 5-RR.

![Figure 5-RR: Venn diagram of quality and compliance through the lens of QRM](image)

In this model, compliance has been wholly encompassed by quality, such that all compliance-related activities likewise add to the quality of the product, and the circle representing quality has been enlarged based on the knowledge gained through QRM. This is the purpose of QRM; in
ensuring compliance supports quality and quality is based on risk management principles and practices, the patient is adequately supported.

A consequence of the misunderstanding of the role of risk management in protecting the patient has manifested with some members of industry claiming to use a “conservative approach” in lieu of QRM. Philosophical dialogues with certain delegates (all of whom worked outside the QRM field) revealed a misunderstanding that QRM need not be used in certain circumstances if a “conservative approach” is employed. One delegate summed up the intent of this term with regard to validation, indicating that he did not apply QRM to determine what and how much to validate, because he validates “everything.” QRM practitioners cringe at this statement, since it indicates a void of knowledge about the purpose of risk management. For example, validating “everything” circumvents any drive to distinguish between critical and non-critical elements, as identified in ICH Q8(R2) and Q11, and therefore dilutes the amount of attention and resources spent assuring that elements critical to the patient are under control—an approach that is certainly not conservative with regard to the patient. It appears that some members of industry perceive QRM as a mechanism to do less, shrinking the amount of resources needed to perform an activity, rather than reallocating available resources to focus more on things that are critical and less on things that are not. This misconception might be a driver behind the Level 3 maturity seen with regard to the purpose of QRM, explored within the governance pillar of QRM.

**Insufficient regulatory guidance combined with overly-prescriptive regulatory requirements**

Many delegates cited the lack of concrete, actionable guidance offered in ICH Q9 and regional regulations adopted from this guideline as a challenge associated with QRM implementation. ICH
Q9 outlines a framework for QRM, and offers examples of how QRM can be applied, but does not provide tactical information regarding *how* QRM can be used to fulfill these purposes. This challenge has been compounded by the eagerness of regulatory authorities to encourage industry to adopt QRM practices, publishing a flurry of requirements to use QRM to accomplish certain deliverables without sufficient guidance on how this should be accomplished within a QRM framework (see excerpts from ICH Q11 discussed in section 2.2.3).

For example, a small group of delegates at the September 2015 PDA/FDA Joint Regulatory Conference met after the day’s activities to discuss how their respective companies planned to implement the (then) recently released EU guideline “on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients for medicinal products for human use.” This document requires the use of a formal risk tool (HACCP is suggested) to determine the rigor of GMP to be *applied* by suppliers of excipients and *enforced* by the drug manufacturer. (91) The document lists eighteen factors to be considered in the risk assessment, as follows:

1. “Transmissible spongiform encephalopathy
2. Potential for viral contamination
3. Potential for microbiological or endotoxin/pyrogen contamination
4. Potential, in general, for any impurity originating from the raw materials, e.g. aflatoxins or pesticides, or generated as part of the process and carried over, e.g. residual solvents and catalysts
5. Sterility assurance for excipients claimed to be sterile
6. Potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities

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7. Environmental control and storage/transportation conditions including cold chain management, if appropriate
8. Supply chain complexity
9. Stability of excipient
10. Packaging integrity evidence
11. The pharmaceutical form and use of the medicinal product containing the excipient
12. The function of the excipient in the formulation, e.g. lubricant in a tablet product or preservative material in a liquid formulation, etc.
13. The proportion of the excipient in the medicinal product composition
14. Daily patient intake of the excipient
15. Any known quality defects/fraudulent adulterations, both globally and at a local company level related to the excipient
16. Whether the excipient is a composite
17. Known or potential impact on the critical quality attributes of the medicinal product
18. Other factors as identified or known to be relevant to assuring patient safety” (91)

The group of delegates lamented the challenges posed by this guideline: the poor fit between many items on the list of required considerations and formal risk tools (including HACCP as the document had suggested), the number of individual risk assessments to be performed (one each per excipient per supplier), and the short timeframe for required implementation (roughly one year from the date of publication). Several delegates agreed that a tool such as risk ranking and filtering (RRF), also described in ICH Q9, would be a better fit than HACCP or FMEA; other delegates pointed out that RRF is typically considered a less formal tool and would not meet the requirement that a “formalized” risk assessment be performed. One delegate expressed his wish that the guideline had simply included the expected format, so he could spend his time executing the approach rather than trying to define it. The informal meeting concluded with no harmonized agreement on the best path forward.
This anecdote is just one example of the struggles reported by QRM practitioners when trying to meet the detailed requirements of regional regulatory bodies within a more fluid, loosely defined QRM framework as offered by ICH Q9. The gap between an overly prescriptive “what” and an insufficiently prescriptive “how” has been identified as one of the obstacles preventing a more mature state to be reached.

**Excessive numbers of risk assessments**

As suggested above, several delegates cited the sheer numbers of risk assessments that have been created as a challenge in achieving a more mature state of QRM. Some delegates noted that regulators appear to expect a discrete risk assessment for every decision or GMP direction in which their companies proceed. Using the above example regarding excipients, a firm with five products, each having four excipients that can be purchased from a mere two qualified suppliers would need to create and periodically review forty risk assessments—just for the relatively narrow risk question regarding the level of GMP required of their excipient suppliers. Indeed, this trend can be seen in other areas as well; regulators expect risk assessments related to elemental impurities as described in ICH Q3D, *Guideline for Elemental Impurities* (92), risk assessments related to viral or other contamination such as those implied (among other sources) in ICH Q5A(R1), *Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* (93) and FDA Guidance *Sterile Drug Products Produced by Aseptic Processing – Good Manufacturing Practice* (94); risk assessments related to cross-contamination such as that suggested by EMA’s *Guideline for setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities* (95); and so on.
These individual, narrowly-construed risk assessments can quickly compound to the point of unmanageability. In December 2009, Wallace Torres at Roche told *The Gold Sheet* that in response to the 2007 public health crisis associated with chemical contamination of their popular HIV drug Viracept, “we performed more than 100,000 full FMEA analyses worldwide in the first year [following the initiation of the company’s QRM program].” (96) Though Torres positioned this as a triumph of QRM implementation, a delegate working for Roche-Genentech noted that excessive numbers of risk assessments can bog down the QRM program and minimize value that can be extracted from the assessments, as time is spent administering to the program is time not spent gaining knowledge. Another delegate expressed regret that her company had not created a QRM deployment strategy when their program started, to help minimize effort while maximizing knowledge gained.

Following the researcher’s presentation of the benchmarking survey results at the PDA Annual Meeting in March 2016, one delegate expressed particular interest in the characterization of industry regarding the targeted vs. holistic approach (discussed with the process pillar of QRM in section 5.2), noting that “the shotgun approach has created a monster.” This is evident not only in regulatory guidance, as noted above, but also in the industry literature. Figure 5-SS illustrates various topics for which QRM approaches are offered in the literature (based upon the mining of sources described in Chapter Two). This “word cloud” varies the text size based on the relative frequency of the topic; there is a wealth of articles on QRM for sterile processing and sterility control, for example, and fewer on QRM for supply chain management. Curiously, there are few if any articles on risk control, risk review, governance, culture, the establishment of a QRM program, or strategic deployment of such a program available in the literature—gaps this research sought to bridge.
Lack of resources to focus on risk management

Many delegates cited a lack of resources, including time and personnel, to focus on risk management as a potential obstacle in the way of further progress. One delegate aptly characterized this concern as a lack of managers’ willingness to deploy resources towards QRM, rather than a lack of availability of these resources. Formal risk management techniques such as Failure Modes and Effects (FMEA) are reported to consume between 40 and 80 hours of work for a team of 6 – 12 people, not including the resources needed to track and implement risk control / mitigation actions. Another delegate indicated the difficulties with allocating resources towards a proactive effort in a fire-fighting culture, where personnel are largely (perhaps habitually) focused on solving existing problems rather than identifying and resolving potential risks. Delegates generally agreed that without concrete ways to measure the effectiveness of QRM activities, such as Key Performance Indicators (KPIs) or financial return-on-investment (ROI), it is difficult to make a case to pursue QRM at the expense of more urgent issues. This challenge is one that will be addressed in Phase 3 of the research.
Fear

It is quite interesting that a primal emotion be listed as an obstacle preventing the successful implementation of QRM; however, this concept did indeed reveal itself in the philosophical dialogues. Many delegates reported a general reluctance within their organizations to embrace the transparency needed to perform QRM tasks, manifesting in several ways:

- Reluctance to analyze products, processes, and systems in a way intended to identify weakness, stemming from the fear that an urgent looming problem would be identified. One delegate likened this to a perception that “what we don’t know can’t hurt us,” pointing out that in most cases, QRM results in more work through the identification of mitigation activities.

- Uneasiness with the idea that, were weaknesses identified and documented, regulators would use the information to assign inspection observations. One delegate compared risk assessments with internal audit reports, which must be completed as part of a larger program but are generally not reviewed by inspectors so as to not discourage a firm from thoroughly identifying actual and potential problems for fear of observations. This delegate believed that risk assessments should be treated similarly, indicating that her firm went so far as to include certain types of risk management documents that should not be presented to inspectors in policy-level documents.

- Discomfort with anticipated differences of opinion between the risk team who created a risk assessment and a third-party reader (whether internal or external to the company). Because QRM is often a subjective endeavor, it ought to be difficult to proclaim its outputs correct or incorrect without data to prove otherwise; however, several delegates indicated that their internal stakeholders often disagree with the analysis performed and conclusions drawn, with one delegate noting that an inspection observation had been received when an inspector believed that certain
“rules” should have been applied to the scoring of individual risks where the risk team had felt otherwise.

Dr. Janet Woodcock, head of the Center of Drug Evaluation and Research (CDER) at FDA, has also expressed concerns regarding a culture of fear, noting:

“Let me just step back another step and say – and this would also disturb some people – that I really think the culture of regulation that we had over the years, [produced] a kind of a fear relationship. And I am still told that industry is in a state of fear, many of them, of FDA. That kind of a fear relationship is not going to grow a quality culture, because there is a fear of adverse consequences… That is antithetical to the idea of a quality culture, where people own quality and say, ‘we can stand up to the FDA because we make a quality product and we know it and we monitor it and we are proud of it. That is our quality culture.’” (97)

The reluctance to embrace QRM based on these fears is indicative of a lack of risk maturity and a struggling company culture; these themes will be explored further in Chapters Seven and Nine.

The learnings from Phase 1 and 2 of the research enabled the researcher to reach several key conclusions, as follows:

- The patient is no better protected following the implementation of ICH Q9 that before,
- Industry has a lower level of risk maturity than might be expected based on the time elapsed since the publication of ICH Q9,
• There are fundamental challenges that are preventing industry from moving towards excellence in QRM, and, most importantly,
• These challenges have solutions.

Prior to endeavoring to define solutions to these problems herself, the researcher realized that a thorough inquiry into other industries with proven track records of successful risk management should be undertaken. Chapter Six, considered to be of the Phase 2 research for the purposes of refining ideas for Phase 3, explores these practices.
Chapter Six: Learning from Risk Management Practices in Other Industries

The research outputs from Phases 1 and 2 revealed the inadequacies inherent with the ways in which the pharmaceutical and biopharmaceutical industries are currently performing QRM. The industry struggles with some basic elements, including robust QRM governance, a proactive culture comprised of engaged leadership and personnel, and the use of QRM in an anticipatory way. Furthermore, there is little evidence that the patient is better protected than before the advent of QRM. Yet there are many industries that have successfully implemented risk management principles and practices to improve their product quality and business practices. This chapter begins with a discussion of ISO 31000, an internal standard on risk management that can be applied to multiple business models, regardless of industry. The chapter continues with the identification and discussion of risk management systems in industries with proven histories of realizing the benefits of the practice. Though examples abound, the researcher selected three such industries for further inquiry: medical devices, aerospace, and nuclear power.

Literature review was selected as the research method for this portion of the research, continuing the literature review first introduced in Chapter Two (as illustrated in Figure 6-A).
Candidate literature was identified primarily through searches of ISO regulations and US government websites for those agencies responsible for the oversight of the applicable industries, including the US National Aeronautics and Space Administration (NASA; www.nasa.gov) and the US Nuclear Regulatory Commission (NRC; www.nrc.gov). Throughout the literature review, the researcher identified key learnings that either:

- Solved a problem related to risk management implementation, as identified in the earlier research
- Filled a gap in risk management application or culture identified in the earlier research, or
• Represented a best practice in risk management that would benefit the pharmaceutical and biopharmaceutical industries and its patients, if implemented

Of these, a subset was selected for discussion in this chapter based on the extent to which it informed the Phase 3 research.

6.1 General risk management – ISO 31000

Prior to 2009, there were a multitude of separate, general-use risk management standards in use across the globe. Individual country authorities had developed and issued their own discrete (yet remarkably similar) documents to help guide companies, irrespective of industry, towards the introduction of risk management principles and processes into their business dealings. (98) Long in practice in several fields, risk management garnered increased attention following the global crisis of 2008, in which ineffective (or inappropriate) risk management practices led to an estimated loss of global wealth of US$34.4 trillion—equivalent to the annual gross domestic product of the United States. (99) (100) Soon thereafter, in 2009, ISO 31000, Risk management – principles and guidelines was published, leading to the retirement of many of the country-specific standards, including the Australia and New Zealand standard AS/NZ 4360, Risk Management, and the Canadian standard CAN/CSA Q850-97, Risk Management: Guideline for Decision Makers.37 While ISO 31000 was in the planning stages far before the economic crisis of 2008, the timing of its release was applauded by regulators the world over. For those familiar with ICH Q9, as

discussed in section 2.2.2 of this thesis, much of ISO 31000 will resonate. There are some meaningful differences, however—ones that provide key learnings for the Phase 3 research.

ISO 31000 outlines benefits beyond those proposed by ICH Q9, articulating principles that address some of the concerns and challenges identified in Phase 1 and 2 of the research. These principles include:

1. “Risk management creates and protects value.
2. Risk management is an integral part of all organizational processes.
3. Risk management is part of decision making.
4. Risk management explicitly addresses uncertainty.
5. Risk management is systematic, structured and timely.
6. Risk management is based on the best available information.
7. Risk management is tailored.
8. Risk management takes human and cultural factors into account.
9. Risk management is transparent and inclusive.
10. Risk management is dynamic, iterative and responsive to change.
11. Risk management fosters continual improvement of the organization.” (15)

While the Phase 3 research, focused on crafting an ideal state for QRM, relied heavily upon each of these principles, this chapter will reflect upon the fourth principle regarding uncertainty—a neglected concept in the world of pharmaceutical and biopharmaceutical QRM.

6.1.1 Learning #1: Acknowledge uncertainty

ICH Q9 briefly addresses the concept of uncertainty and its role in QRM as follows:
“In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.” (45)

The differences in emphasis on uncertainty—as fundamental to risk management in ISO 31000, yet a small note positioned under risk assessment in ICH Q9—may have contributed to the differences in risk maturity within the pharmaceutical and biopharmaceutical industries and other industries as explored in this chapter. This difference in emphasis is inherent in the very definition of “risk”.

As presented in section 1.2 and as reiterated in ICH Q9, the term “risk” is defined as an equation whereby:

\[
\text{Likelihood (of the occurrence of harm) \times Severity (of that harm) = Risk}
\]

This definition of risk is presented in ICH Q9 and ISO 14971 for medical devices, both of which are focused on patient safety through the realization of medical products (drugs and devices, respectively). Suitably, the origin of this definition is the ISO Guide 51, \textit{Safety aspects – Guidelines for their inclusion in standards}, a document which itself describes risk management
as a means to achieve product safety. (45) (101) (16) ISO 31000, however, offers an alternate
definition of risk— “the effect of uncertainty on objectives.” (15)

This definition allows the very concept of risk to be reimagined in the context of drug
manufacturing. Rather than an equation that implies precise measurements of risk can be made,
the definition of risk in ISO 31000\(^ {38} \), applied to the pharmaceutical and biopharmaceutical
industries, can be framed as the effect of uncertainty on the patient. Using the ISO 31000
definition, the goal of QRM therefore can be positioned as one of minimizing uncertainty
associated with the product and the associated manufacturing process in order to better protect
the patient. This would encourage industry to seek out knowledge in the form of deeper and
more meaningful scientific analysis, rather than attempting to predict the likelihood of a given
hazard or harm based on incomplete evidence or a cursory interpretation of available data. Only
a small number of published QRM methods, including the CQA identification approach
described in PDA Technical Report No. 60 and the risk-based impact assessment tool offered by
Waldron, explicitly include measures of uncertainty (or conversely, in statistical terms,
confidence) within the risk assessment process. (102) (103) The pharmaceutical and
biopharmaceutical industries would benefit from placing more of an emphasis on disclosing,
reducing, and thinking critically about sources and levels of uncertainty associated with the
scientific knowledge that underpins QRM.

\(^ {38} \) The definition of risk from ISO 31000 is in turn derived from ISO Guide 73, Risk management – vocabulary, which
endeavored to bring a common vernacular to all forms of risk management, including those related to safety as defined
in ISO Guide 51. (14) Based on the breadth of terminology currently in use across industries of all types, and the
preservation of different terms and definitions in a variety of risk management standards, it appears as through a
harmonized risk management language has yet to take hold.
6.1.2 Learning #2: Define the context

The risk management lifecycle depicted in ISO 31000 (shown in Figure 6-B) echoes that of ICH Q9 (described in section 2.2.2), and includes the fundamental phases of risk assessment, risk treatment/control\textsuperscript{39}, review of the risks given new knowledge, and communication of the risks.

\textbf{Figure 6-B: Risk Management Lifecycle from ISO 31000:2009}

\textsuperscript{39} “Risk treatment” in ISO 31000 replaces the “risk control” step in ICH Q9. While the concepts are fundamentally the same—taking action based on the learnings from the risk assessment—“risk treatment” could include additional actions to embrace and pursue risks (opportunities) while “risk control” is focused on reducing and controlling the risk. This difference stems from the perspective of each document, with ICH Q9 focusing on negative risks to product quality and patient safety and ISO 31000 addressing risks of all types, both positive and negative. Because some quality risks may be reduced through the introduction of new, positive risks (such as those associated with the introduction of new technology that carries with it a high level of uncertainty), this researcher prefers the term “risk treatment” over “risk control.” However, to preserve the terminology used in this thesis to this point and for fidelity with ICH Q9, the term “risk control” will continue to be used.
Despite the similarities between these risk management lifecycle, the initiating step of ISO 31000 stands out—a step called “establishing the context.” The ISO standard devotes a large portion of the document to the explanation and reinforcement of this critical step, one in which the internal and external business climate are carefully evaluated to ensure subsequent risk management activities are aligned with the environment in which they are performed. In the pharmaceutical and biopharmaceutical industries, “establishing the context” might entail a critical analysis of internal conditions such as:

- The availability of scientific knowledge to adequately assess the risks
- The expertise and competencies necessary to perform risk management activities,
- The resources available to assess and reduce the risk, where necessary
- The type of medicinal product under evaluation (e.g. life-saving, life-sustaining, quality-of-life),
- The vulnerability of the product to shortage, and
- The company’s risk tolerance

In addition, conditions external to the company should also be identified and evaluated, such as:

- Applicable laws and regulations in the markets for which the product is intended
- The vulnerability of the patient community in the event of a drug shortage
- Perceptions of risk in the regulatory and patient community
- Regulatory authorities’ risk tolerance(s)
- The patients’ risk tolerance(s)

Indeed, the internal and external perspectives that may result from such a careful analysis of the context could significantly affect the QRM process and outcomes. It is for this reason that ISO
31000 notes, “…attention to these and other relevant factors should help ensure that the risk management approach adopted is appropriate to the circumstances, to the organization and to the risks affecting the achievement of its objectives.” (15) A robust review of the internal and external climate in which QRM activities are being conducted will ensure that such exercises better protect the patient.

6.2 Risk management in the medical device industry

The medical device industry has long felt the influence of risk management principles, having been subject to risk-based classification and regulation since the term “medical device” was formally defined.40 Risk management as part of medical device development and manufacture was introduced in the EU in 1993 with the issuance of the Medical Device Directive, 93/42/EEC, which included a clear statement in the first General Requirement that “…devices must be designed and manufactured in such a way that…any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.” (104) This concept took hold in the US with the issuance of FDA’s Design Control Guidance in 1997, and a harmonized method for performing risk management for medical devices was published in 2000 with the first version of ISO 14971, Medical devices –risk management for medical devices. (101) (105) ISO 14971 has some remarkably similarities to ICH Q9, but it is the differences between the two that lead to insight.

40 The US FDA “Medical Device Amendments” of May 28, 1976 introduced the classification of devices as Class I (low risk), Class II (moderate risk), and Class III (high risk) based on the potential to harm the patient and the level of control required to assure safety and effectiveness of the device. Prior to this date, there was no harmonized definition for a medical device in the US and therefore no risk-based classification scheme. (197) Device classification remains risk based in major markets and is currently performed according to 21CFR860 in the US and 93/42/EEC in the EU. (198) (199)
6.2.1 Learning #3: Focus on the product

Unlike ICH Q9, which is focused on the management of extrinsic risks, medical device risk management is primarily concerned with the management of intrinsic risks. For example, ISO 14971 notes in its introduction, “The requirements contained in this International Standard provide manufacturers with a framework within which experience, insight and judgment are applied systematically to manage the risks associated with the use of medical devices” [emphasis added]. (101) ICH Q9, on the other hand, limits its scope to “aspects of pharmaceutical quality” and acknowledges that “the risk to [the drug’s] quality is just one component of the overall risk.” (45) The other risks referred to in this quote include intrinsic risks associated with the use of pharmaceuticals and biopharmaceuticals, such as those described in Chapter One.

Devices and drug products differ fundamentally with regard to intrinsic risks—while drugs often have inherent side effects and contraindications that manifest as a result of biochemical processes in vivo and are associated with the target molecule or biological pathway itself, intrinsic risks associated with medical devices can often be designed out of the product through the use of engineering principles.41 The differences between product designed through chemistry and biology and those designed through engineering may contribute to the differences in emphasis seen between ISO 14971, with a distinctly product perspective to risk management, and ICH Q9, with a product quality and quality systems perspective.

41 It is worth noting that emerging therapeutic modalities in the biopharmaceutical industry, such as gene therapies, cellular therapies, and personalized medicines, are seeing the scientific fields of biology and chemistry merge with engineering with regard to product development. In this researcher’s opinion, for medicinal therapies that allow for engineering principles to be applied (e.g. gene editing), a medical device risk management perspective and regulatory framework might be better suited than the existing drug perspective due to the opportunity to eliminate many intrinsic risks, thereby directly increasing patient protection.
During medical device development, firms often create three separate risk assessments to address the requirements of ISO 14971 and similar device regulation: a design risk assessment, addressing risks associated with the design of the device, an application risk assessment, addressing risks associated with the healthcare practitioners’ handling of the device, and a process risk assessment, addressing risk associated with the manufacture of the device. (101) (106) When subject to the process steps defined in the risk management lifecycle, these three risk assessments cover a majority of the risk-related concerns for medical devices. These risk assessments are stored in a “risk management file” specific to the medical device or family of devices. (101) In this way, ISO 14971 has fostered the creation of a sort of “living risk assessment library” that can be used as a reference tool for knowledge management as well as streamlined summary of the major risks associated with a given device.

With only 54.6% of benchmarking survey respondents reporting the consistent application of QRM to product and process characterization (as discussed in section 5.2.2), it seems unlikely that the concept and value of a living risk library, akin to the risk management file approach used in medical devices, has fully penetrated the pharmaceutical and biopharmaceutical industries. The design and creation of such a library is discussed further in Chapter Eight.

6.2.2 Learning #4: Risk control deserves the most attention

Though no documents have been located by the researcher, to date, that expressly point to one phase of the risk management lifecycle as more important than the others, the regulatory and quality foundation upon which drug manufacturing occurs make this answer an obvious one: controlling risks to patient should be the primary focus of any QRM endeavor. Detailed, science-
based risk assessments, robust risk review, and frequent and transparent risk communication serve little purpose if the patient is not ultimately better protected in the end. Risk control is the step at which the patient experience benefits. It is the step during which control measures are established to address identified risks, leader to better quality product and, therefore, a safer patient.

While ICH Q9 dedicates only a few cursory paragraphs to the topic, ISO 14971 devotes several pages to explaining the objectives of risk control, techniques to enable more effective control over risks to the patient, and the rationale behind these requirements. (101) The emphasis placed on risk control is evident with a review of the risk management lifecycle for medical devices (Figure 6-C), which denotes six sub-steps to what constitutes a single sub-step (“risk reduction”) in ICH Q9. ISO 14971 seeks to ensure that the reader understands the importance, and the relative amount of attention, that should be paid to reducing risk to the patient.

In ISO 14971, the risk reduction process begins with a thorough examination of available options for risk control, and comparing these options to determine the best fit to reduce a particular risk or portfolio of risks. Risk reduction measures, or mitigations, must be both technological and economically feasible42 and be designed to reduce the risk as low as possible. The standard

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42 The topic of “economic feasibility” has been of much debate since the publication of the 2012 revision to ISO 14971, which did not alter the content of the standard itself but instead updated Annexes Z-A through Z-C which reconcile the requirements of the standard with those of the EU Medical Device Directive (MDD). The MDD does not, in letter or spirit, include an allowance to disregard a risk control option due to its cost; therefore the Annexes were updated to note that economic factors may not be a factor in selecting risk reduction options for those devices intended to registered in the EU. (100) However, in the current era where drug pricing has become a heated political and practical issue, manufacturers are reluctant to apply risk reduction measures that may render the cost of treatment out of reach for patients. It is this researcher’s opinion that the topic of economic feasibility is an important one that requires additional discussion, outside of the realm of this thesis. As such, the researcher has chosen to preserve the requirement that a risk reduction strategy must be economically feasible in order to be effective and reach the patients.
Figure 6-C: Risk Management Lifecycle from ISO 14971:2009
requires one to consider the effect a given risk reduction option may have on the risk as well, listing a priority of “(a) inherent safety by design, (b) protective measures in the medical device itself or in the manufacturing process, [and] (c) information for safety.” (101) This order lists control options from most to least effective, with elimination of risk through system or product design being most effective at patient protection, followed by risk mitigation by reducing the likelihood of harm, and finally informing patients and users of the risks and appropriate control measures to be applied through risk communication.

Once the options for risk control have been identified, analyzed, and compared, the best fit option (or combination of options) is selected for implementation. ISO 14971 requires that, once the risk control measures are in place, they be verified—twice. The first verification confirms that the control measure has, in fact, been implemented, while the second verifies effectiveness by determining that the risk has actually been lowered. (101) In most instances, because the risks are intrinsic to the product, effectiveness can be confirmed through design validation of the device itself; it may prove more difficult to measure risk reduction for other types of risks and related controls, particularly for proactively identified risks that have not been historically realized. (107)

Once all risk control measures have been fully verified, ISO 14971 requires the residual risk to be determined. (101) This process includes an evaluation of whether new risks have been introduced as a result of the risk control measures, and a determination of the new risk levels in light of the additional controls. The acceptability of the residual risk is determined through a comparison of the risk level against pre-defined criteria—a similar process as was employed when determining which risks required reduction. ISO 14971 goes further however, acknowledging that where the residual risk remains unacceptable, a risk/benefit analysis should be performed. This risk/benefit
analysis seeks to compare the medical benefits of the device against the (individual) residual risk to determine whether, on balance, the patient is adequately protected. This individual risk/benefit analysis often serves as an input into risk communication, assisting the manufacturer with the design of product labeling to disclose such risks to the consumer. (101) (108)

Per ISO 14971, once the individual risk/benefit analyses are complete, a second, overall risk/benefit analysis is performed to determine whether the cumulative effects of all residual risks associated with the device are outweighed by its benefits to the patient. (101) This step, absent in ICH Q9, requires the risk practitioner to evaluate and understand the totality of risk to which the patient is subjected through use of the product. Only where the device offers a greater benefit to the patient than it does risk is the overall residual risk deemed acceptable. This process facilitates a strategic view of the complete risk portfolio, requiring the practitioner to redirect their attention from detailed line items captured in a spreadsheet back to the ultimate goal—protecting the patient.

ISO 14971 acknowledges the paramount importance of risk control in the risk management lifecycle, and refocuses attention from what might often be an intellectual endeavor to the patient. The pharmaceutical and biopharmaceutical industries would benefit from the adoption of these practices in their QRM work.

6.2.3 Learning #5: Planning is key

ISO 14971 describes the use of a Risk Management Plan for device risk management. Unlike the Risk Management Plan designed to manage intrinsic drug risks, as discussed in Chapter One, this document is intended to outline the plan for risk management activities in support of device
development and manufacturing. As noted by ISO 14971, “a risk management plan is required because (a) an organized approach is essential for good risk management, (b) the plan provides the roadmap for risk management, [and] (c) the plan encourages objectivity and helps prevent essential elements from being forgotten.” (101)

The requirements for a Risk Management Plan read similar to what one might envision as a QRM procedure for the pharmaceutical and biopharmaceutical industries. Role and responsibilities are defined and delineated, the scope of the plan with regard to the product lifecycle is outlined, a governance structure and associated processes are established, risk and residual risk acceptance criteria are defined, and requirements and data sources for the use of production and post-production information (similar to the risk review phase of the ICH Q9 lifecycle) are described. (101) In addition to these standard requirements, ISO 14971 notes that the Risk Management Plan may be used to define milestones, plan risk management activities, and outline risk tools that will be employed for the various activities. In this way, the Risk Management Plan has an inherently flexible structure with the goal of better enabling the organization to plan for what risk management activities must be done to align with certain product-realization goals.

ICH Q9 contains no notion of a Risk Management Plan. There is an assumption that a QRM procedure or policy-level document would exist, of course, as is a general quality system requirement in those regions that have adopted the guidance. (45) However, the idea that a firm should outline strategic goals for the QRM program and develop a plan to reach them is notably absent. This is a plausible reason why the industry has struggled with the administration of the QRM program and the creation of myriad risk assessments with no holistic vision, as discussed in Chapter Five—in the absence of planning, the ICH Q9 lifecycle begins with a “QRM Initiation”
step, the focus of which is a rather myopic process to gather the information needed to begin a risk assessment and continue throughout the QRM lifecycle. ISO 14971 has no need for this initiation step, as all risk management activities would be pre-defined in the Risk Management Plan and need merely be executed in accordance with those requirements. By streamlining the initiation process and outlining overarching objectives for the QRM program, the use of a Risk Management Plan would enable the pharmaceutical and biopharmaceutical industries to spend less time “doing QRM” and more time managing risk to the patient.

6.3  Risk management in the aerospace industry

The aerospace industry has a history of highly publicized successes, where the application of risk management principles and practices have enabled monumental discoveries unprecedented in human history, as well as shocking disasters that have led nations to mourning. The need for risk management in aerospace is clear: the risks associated with an environment that is completely beyond control, the (literally) astronomical costs associated with developing the technology to achieve spaceflight, and the shortage of opportunities to use that technology mandate that risks be understood and manage to achieve right-first-time missions—because in aerospace, the first time may be the only time.

6.3.1 Learning #6: Acknowledge the two objectives of risk management

The US National Aeronautics and Space Agency is generous with their learnings and operational practices, offering many of their internal guidebooks and operational manuals to the public from their website, www.nasa.gov. The risk management process in use at the agency is summarized in the NASA Risk Management Handbook, issued by the Office of Safety and Mission Assurance.
The handbook details risk management tools and decision-making frameworks, and provides instructions on establishing performance-based risk tolerance, modeling and graphical representation of risks, probabilistic risk assessment (PRA) techniques\(^ {43} \), and risk control planning. Perhaps the most influential learning from NASA’s risk management program, however, is the way in which the agency has divided risk management into two sub-processes: risk-informed decision making (RIDM) and continuous risk management (CRM). (109)

At NASA, CRM mirrors the risk management process as described thus far in this thesis. Risks are identified, assessed, controlled, and reviewed in an iterative framework to ensure risks to the success of a space mission and the safety and security of the astronauts and payloads are continually evaluated, with risk controls designed in as engineering solutions. The risks and scenarios in which they may manifest are communicated throughout the agency, from the technical experts through the top-levels elected officials who are responsible for the overall performance of the agency. (109) In this way, the CRM process at NASA is similar to the QRM lifecycle described in ICH Q9.

NASA, however, has acknowledged a separate risk management process that does not follow the risk management lifecycle in full—this process, risk-informed decision making, is a necessary component of robust risk management with its own process and objectives. Figure 6-D illustrates

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\(^{43}\) Probabilistic Risk Assessment is the name given to a series of risk management tools, including master logic diagrams, event sequence diagrams, fault tree analyses, and Monte Carlo simulations, used in concert to yield a result. PRA appears to be the preferred risk assessment approach for NASA and the US Nuclear Regulatory Commission (NRC), both of which have multiple handbooks available the public sphere regarding the method and its merits. (259) (259) (186) The researcher chose not to include a detailed analysis of PRA in this thesis because the approach hinges upon mathematical models that continue to elude the pharmaceutical and biopharmaceutical industries, which, as discussed in section 6.1.1, are still struggling with uncertainty in some of the fundamental science inherent in drug products and their manufacture. Chapter Eleven includes inquiry into PRA as a topic for future work in the QRM field.
the process steps involved with risk-informed decision making. RIDM begins with the identification of alternatives—that is, the potential decisions that could be made. A risk analysis is then performed on each of the alternatives to enable a comparison of risks associated with each decision path. Finally, considering the results of risk analyses (assessments) and other considerations, such as the benefits offered by each potential decision path, the decision is taken. The risk assessments performed to support the decision-making process are not subject to other aspects of the risk management lifecycle, such as risk control or risk review. Rather, the risk assessment was performed for the express purpose of enabling a specific decision to be made at a specific point in time, using the best available information at the time. Once the decision is made, the risk assessment has served its purpose.

Figure 6-D: NASA’s Risk-Informed Decision Making (RIDM) Process (108)
These sorts of *ad hoc* risk assessments have utility in the pharmaceutical and biopharmaceutical industries as well. Decisions regarding product release in the face of a cGMP deviation, whether to proceed with a proposed change to the manufacturing process, the frequency and scope of internal or supplier audits, and other operational, quality, and compliance related decisions are made every day by drug manufacturers. Do each of these decisions require a risk assessment to inform them? As NASA’s *Risk-Informed Decision Making Handbook* explains:

“[Decisions for which RIDM is appropriate] tend to have one or more of the following characteristics:

- **High Stakes** — High stakes are involved in the decision, such as significant costs, significant potential safety impacts, or the importance of meeting the objectives.
- **Complexity** — The actual ramifications of alternatives are difficult to understand without detailed analysis.
- **Uncertainty** — Uncertainty in key inputs creates substantial uncertainty in the outcome of the decision alternatives and points to risks that may need to be managed.
- **Multiple Attributes** — Greater numbers of attributes cause a greater need for formal analysis.
- **Diversity of Stakeholders** — Extra attention is warranted to clarify objectives and formulate performance measures when the set of stakeholders reflects a diversity of values, preferences, and perspectives.” (110)

The use of *ad hoc* risk assessments for risk-based decision making in the pharmaceutical and biopharmaceutical industries would allow for more context-specific risk questions to be established while alleviating some of the administrative burden reported by QRM practitioners in the earlier research.
6.3.2 Learning #7: “Complacency is the enemy of quality”

While NASA’s many successes highlight the critical role risk management fills, the failures experienced by the agency offer similar lessons. The story of two of the most stunning disasters in the history of space exploration—the explosion of the Challenger mission within moments of launch and the breakup of the Columbia spacecraft upon reentry to Earth—reveal an important element regarding the culture in which risk management is applied.

On January 28, 1986, the Challenger mission began. News outlets across the world broadcasted the launch to the public, many of whom sat with bated breath in front of their television sets to watch their newly-minted heroes begin their exploration into the solar system. A mere 72 seconds after lifting off, a plume of smoke could be seen. Moments later, Challenger burst apart, the result of an explosion caused by faulty seals in the shuttle construct. Most of the world was shocked. Many at NASA were not. (111) (112) (113)

Engineers at NASA had predicted the event. They had inspected O-rings, the seals that connect the rocket boosters to the spacecraft, on numerous occasions following prior missions, and were aware of the erosion that occurred, destabilizing the connection and threatening the integrity of the hull. They had accounted for this phenomenon in their PRAs, noting in particular that cold weather could render the O-rings so brittle that they would fail almost immediately, leaving no chance for the spacecraft to remain intact. They had discussed the results of their risk assessments with NASA decision-makers, and, noting the freezing temperatures predicted for the Challenger launch day,

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44 Quote attributed to Rick Friedman, Deputy Director of Science and Regulatory Policy, Office of Manufacturing Quality, FDA
recommended the mission be delayed. Yet the mission proceeded, and lives were lost. It was a failure of risk management on the world stage. (111) (112) (113)

Seventeen years later, an eerily similar event occurred. This time, it was the shuttle Columbia, and it was the end of the mission. The public awaited the reentry of the spacecraft into Earth’s atmosphere, ready to celebrate the returning astronauts with parades and news interviews. Not quite two minutes after reentry, the shuttle burst apart, the result of damage to the left wing caused by impact with a piece of foam that had dislodged during launch. Again, the public was shocked, and again, NASA was not. NASA engineers became aware of the impact the day after launch, during the routine video footage review and analysis intended to prevent failures of this type. Mission Control informed the crew of Columbia, asserting that the event was of no consequence and there should be no concern regarding the safety or integrity of the spacecraft. After all, they had seen this before on successful missions. (114) (115)

Despite their initial conclusion, NASA proceed to evaluate the impact event, though under the caution that it was an “information gathering” endeavor—not one that was critical to the safety of the mission. They gathered their best and brightest, who began to apply proven risk management techniques and mathematical modelling to confirm their original assumption—that the impact to the left wing would not jeopardize the shuttle upon reentry. The engineers, however, did not have enough information from the original launch footage to perform a thorough analysis. They needed, and requested, more information. Their request was discussed by NASA management, but no action was taken—the risk associated with the impact of the foam on the left wing was deemed
acceptable.\textsuperscript{45} No interventions were made. Upon reentry, the shuttle and the lives of those within it were destroyed. (114) (115) The “acceptable risk” proved to be anything but—risk management had again failed at NASA.

As one might expect, post-mortem analyses following both the Challenger and Columbia disasters were as plentiful as they were critical. Most sources agree that risk management had failed in these instances, as well as the reason it had failed; the risk management activities were conducted within a culture that, at that time, was complacent and did not learn from its mistakes. Without a stronger culture, risk management was destined to fail.

The primary cultural element that contributed to these failures is one that is also ubiquitous in the pharmaceutical and biopharmaceutical industries: the “normalization of deviance.” (116) Normalization of deviance is a phenomenon in which an organization becomes numb to failures that occur on a regular basis. Because there are often no catastrophic consequences that occur from these failures, the organization accepts them as a normal part of operations and becomes complacent with their occurrence. (117) Such a culture is widespread in the drug industry, as quality leaders cite process deviations as “normal” with a willingness to accept a certain (non-zero) number. This cultural norm, where failure is accepted by the organization, is anathema with regard to the goals to risk management—continual improvement and a proactive, risk avoidant mindset.

\textsuperscript{45} The additional data needed was satellite footage of the shuttle during its mission, which would have allowed the risk management team to better understand the angle of impact—knowledge critical to understanding the risks that were posed. The US Department of Defense had historically provided such footage upon request, but given the “acceptable” classification of the risk associated with the Columbia event, a request was not made. (108)
6.4 Risk management in the nuclear industry

The final industry chosen as a best practice benchmark for risk management is the nuclear industry. Nuclear power is perhaps best known for its adaptation of a military technique known as defense in depth to risk management, particularly in the area of risk control. Defense in depth holds that multiple layers of risk control should be employed in concert, so that control over the risks associated with a system should never depend upon a single control, lest it fail and the risk be realized. The US NRC states, “the key [to defense in depth] is creating multiple independent and redundant layers of defense to compensate for potential human and mechanical failures so that no single layer, no matter how robust, is exclusively relied upon. Defense in depth includes the use of access controls, physical barriers, redundant and diverse key safety functions, and emergency response measures.” (118)

The use of multiple control layers is not a foreign concept, although the nuclear industry employs it with excellence. A metaphor for risk management known as the “Swiss cheese model” was initially conceived by James Reason in 1990, and has become ubiquitous across multiple academic and industry risk management circles. (119) (120) This model holds that accidents happen (or risk are realized) when “holes” in “barriers” (i.e. risk controls), such as vulnerability points or failures, occur in tandem, allowing a hazard to reach the patient and cause harm. This model is typically depicted in graphic form as shown in Figure 6-E, hence the “Swiss cheese” moniker.
Using the Swiss cheese model, the objective of risk control is to construct barriers for which the holes will never overlap—that is, that are not so tightly coupled that a single point of failure would lead to the failure of all of the barriers.

In the nuclear industry, these barriers form the core of the defense in depth system. There are typically five barrier layers in a nuclear reactor system to manage the risks of reactor meltdown and any resultant radioactive fallout:

1. “Prevention of abnormal operation and failures
2. Control of abnormal operation and detection of failures
3. Control of accidents within the design basis
4. Control of severe plant conditions [to prevent accident progression and to mitigate the consequences of accidents]
5. Mitigation of radiological consequences of significant release of radioactive material.” (121)
In the pharmaceutical and biopharmaceutical industries, many of these barriers are inherent in quality system requirements and may be rephrased as:

1. Eliminate or prevent quality risks through the use of QRM
2. Detect quality risks through QRM and process/product monitoring
3. Manage deviations when quality risks occur
4. Manage the consequences of the deviation through disposition of affected product
5. Manage consequences to the patient through recall and patient support

In a robust quality system, including the application of effective QRM principles and practices, the defense in depth concept can be applied to ensure the patient is protected.46

6.4.1 Learning #8: Communicate with purpose

“[In the eyes of the public], risk = hazard + outrage.” (122) This quote, drawing a playful juxtaposition with the notorious risk = likelihood x severity equation that permeates risk management, sets the stage for the US NRC’s handbook on external risk communication. The topic, of course, is a serious one—how to frame risks and their criticality to a third party who lacks the intimate scientific knowledge that the communicator possesses. In the realm of nuclear reactors, any accident or hazard is likely to be met with fear and indignation from the public. The consequences of a nuclear meltdown affect not only the people living and working in the vicinity

46 The reader may question why the researcher has not chosen to identify defense in depth as one of the key learnings in this chapter; therefore it is important to proactively address this concern. The researcher acknowledges that additional research into the application of defense in depth principles would be beneficial for industry. However, the research effort is focused on the application of quality risk management in a proactive way (numbered items 1 and 2) in the list), and the researcher is loath to extend the scope of the research to include reactive risk and crisis management (numbered items 3 through 5 in the list). While the topic of defense in depth and its utility in the pharmaceutical and biopharmaceutical industries piques the researcher’s interest, she must relegate further discussion on the topic to Chapter Eleven.
of the accident, but also their children and their children’s children. The severity scale for nuclear disasters can be measured in generations, and risk management must be held proportionately sacrosanct.

While risk management forms the core of nuclear industry operations, risk communication is most often performed by its regulators, including the NRC in the United States. As discussed in Chapter Two, risk communication occurs between the communicator and internal and external stakeholders. The NRC understands the emotional aspects of communication and the consequences of miscommunication (or a lack of communication), and has therefore ensured that communication with the public regarding risks associated with the nuclear industry are thoroughly planned and controlled, and that all NRC employees are equipped to speak on behalf of the agency when called upon. (122) These principles and the process for effective risk communication to the public is summarized in NUREG/BR-0308, “Effective Risk Communication: The Nuclear Regulatory Commission’s Guidelines for External Risk Communication,” a handbook for all staff to use. In addition, the NRC has a created a sister document, NUREG/BR-0318, “Effective Risk Communication: Guidelines for Internal Communication.” (123) This document acknowledges the importance of knowledge sharing and communication regarding identified and analyzed risks within the NRC, as well as resultant decisions and policy changes. The processes defined by the NRC for internal and external risk communication are shown in consolidated format in Figure 6-F.
The NRC has assigned the first step in successful risk communication, whether internal or external, as “establish objectives.” For the NRC, there may be several objectives associated with internal risk communication, such as:

- Gathering information to assist with a risk assessment
• Seeking peer feedback or input
• Providing input that may contribute to a decision
• Providing background information
• Conveying a decision
• Building consensus or resolving issues
• Supporting communication with external stakeholders, and/or
• Developing a risk-informed, performance based assessment in a new area (123)

With regard to external risk communication, the objectives may be:

• Providing information
• Gathering information
• Building trust and credibility
• Seeking involvement, and/or
• Influencing behavior or perceptions about risk (122)

Within the pharmaceutical and biopharmaceutical industries, these lists might be combined, as they represent common objectives irrespective of whether the stakeholder is internal or external. For example, a drug manufacturer may communicate externally to regulators regarding decisions that have been made based on QRM, while an individual QRM practitioner may wish to build trust and credibility regarding identified risks internally with his or her leadership, staff, or peers.

With the objectives for risk communication established, the process reaches the planning stage. This begins with the identification of stakeholders and a careful evaluation of their potential concerns, preconceptions, and existing knowledge regarding the risks or risk topics being communicated. The stakeholders will be the recipients of the risk communication, and must be
thoroughly understood in order for the communication to be effective. Any imbalances in knowledge and underlying bias should be explicitly addressed in the communication plan, and risk communication methods should be selected to ensure that the risk information being communicated is clear to the intended audience. (122) (123)

Preparation follows the planning stage, and entails the creation of communication materials (such as slides, speaker notes, email messages, or letters), the anticipation of potential questions or points of contention, and the collation of information and data to support key messages. Finally, the communication occurs; this may be passive communication, as may be the case when the objective is to inform the recipient of facts or decisions, or it may be an active dialogue requiring the use of active listening skills. Once the communication has occurred, the communicator should reflect on the experience and identify opportunities for improvement in the future. (122) (123)

While the above discourse on effective risk communication can be viewed as “good communication practices” in a general sense, the fact that these principles are applied in a disciplined way to the communication of risk information within the nuclear industry is not inconsequential. There is an entire field of study and related body of literature dedicated to how risk is perceived by individuals47, and the recipient’s state of mind and frame of reference can greatly influence their interpretation of both the information and message communicated. (124) In order for the risk information to be transmitted from sender to receiver in the way in which it was intended, risk communication must not be marginalized or taken for granted. This is particularly

47 The most notable of these is the work of Kahneman and Tversky on human heuristics and cognitive biases.
true of QRM in the pharmaceutical and biopharmaceutical industries, where the risk information directly affects the life and health of patients.

Equipped with best practices and key lessons from industries with a history of effective risk management implementation, the research reached its third and final phase. This phase, documented in Section Three (Chapters Seven through Ten), focused on synthesizing the learnings from Phase 1 and 2 of the research with additional research to define the ideal state of QRM: a state in which QRM truly enables the pharmaceutical and biopharmaceutical industries to manage risk to the patient.
Section Three: Recoding QRM to Better Manage Risk to the Patient
“Everything should be made as simple as possible, but no simpler.”

- Albert Einstein

“There is nothing about risk management that does not make common sense.”

- Amanda Bishop McFarland
7 Chapter Seven: What QRM Maturity Looks Like - People

This chapter marks the first of three aimed at characterizing the ideal state of QRM—a state in which a firm’s QRM program has been optimized to provide the maximum benefit to both the company and the patient.

7.1 Research design and process for Chapters Seven, Eight, and Nine

The Phase 3 research discussed in Chapters Seven, Eight, and Nine represents a synthesis of prior learnings and phase-specific qualitative research methods, as introduced in Chapter Three. A combination of philosophical dialogues, literature review, and semi-structured interviews were used. Philosophical dialogues took place primarily at industry conferences, such as those sponsored by PDA and IVT, which were attended by large groups of delegates with varying levels of expertise and practical experience in QRM. The researcher sought out specific individuals to discuss QRM topics based on their current roles, and leveraged delegates attending conference sessions on or relating to QRM topics. Themes were identified and later trended, and selected quotes were documented by the researcher during these exchanges. In many cases, the themes that emerged from the philosophical dialogues echoed the researcher’s own experience and learnings from the Phase 1 and 2 research; these are cited accordingly in the chapters that follow.

The literature review consisted of articles from industry periodicals, peer-reviewed journals, and reports, as discussed in Chapter Two of this thesis and as shown in Figure 7-A. In addition, the researcher incorporated several books on quality and risk management topics, as well as whitepapers and reports published by renowned consulting firms (such as Deloitte and Price
Waterhouse Coopers) and risk management-related organizations (such as the Risk Management Society, or RIMS, and the Committee of Sponsoring Organizations of the Treadway Commission, or COSO). The literature review therefore extended beyond QRM in the pharmaceutical and biopharmaceutical industries to other industries, such as finance and insurance, and other risk management fields, such as Enterprise Risk Management (ERM). These sources added depth to the Phase 3 research and enabled the characterizing of best practices from a variety of trades, further expanding upon the industries selected for the Phase 2 research in Chapter Six.

Figure 7-A: Literature map highlighting focus for Chapters Seven, Eight, and Nine
As noted in Chapter Three, the semi-structured interviews of QRM experts were conducted either in person, via telephone, or via written correspondence in instances where the experts’ schedules were not conducive to a dialogue. Each expert was asked to review a research brief, prepared in accordance with the DIT’s rules for ethical research conduct and approved by the Ethics Committee, and sign a declaration that they agreed to serve as research subject. In person and phone interviews were recorded and later transcribed. Each transcript (or written interview response) was coded for key words and analyzed to inform the applicable topic in Chapters Seven, Eight, and Nine. These semi-structured interviews found many themes, as well as some disparate opinions that offered a richness to the research.

This chapter intends to characterize maturity with regard to the people pillar of QRM and is divided into three sections. The first section discusses the benefits of, and methods for, building awareness of QRM principles and practices throughout industry, as embodied within those personnel working at a given pharmaceutical and biopharmaceutical manufacturing site. The second section discusses the need for building expertise within industry for QRM as a discipline in its own right, and offers an educational approach to achieve this. The third and final section of this chapter explores risk culture, including those characteristics indicative of mature and immature risk cultures, and summarizes some best practices to enhance risk culture.

7.2 Building organizational awareness of QRM

A common theme identified in the benchmarking survey, expert interviews, and literature review is the need for all employees to possess a basic level of awareness of QRM, irrespective of their individual job responsibilities. Because QRM is an enabler of the quality system, and all employees are responsible for ensuring the quality of the products they manufacture or support, an
understanding of QRM principles and practices throughout each organization is necessary. However, O’Donnell summarizes that currently, “[most] people [in the pharmaceutical and biopharmaceutical industries] don’t make the links between what they do and QRM.” (125)

Ramnarine notes that at companies mature in QRM, individuals at all levels and functions are able to identify and communicate risks associated with their daily work. (126) Vesper reiterates this, noting that firms mature in QRM implementation will have developed their staff such that “…people think about risks as part of their job. They understand risks associated with their job, and they realize that before they start a task, they should run through it in their mind, [and ask] what can go wrong here? What will I do if it goes downhill? Where am I vulnerable in this particular activity? So it’s where risk is a natural part of daily work. It’s risk-based thinking.” (127) Developing an organization that easily identifies risk and seamlessly integrates QRM principles into task preparation and execution provides a competitive advantage to drug manufacturers and a direct benefit to patients. The risk-aware mindset allows for potential issues to be more readily identified and remediated in real time, before consequences on product quality manifest.

In order to develop the appropriate level of organizational awareness of QRM, companies with mature QRM programs often employ role-based training. (128) (129) (130) This model enables a tailored approach to QRM knowledge transfer based on an individual’s level of interaction with QRM. While certain roles may require minimal technical knowledge of QRM, those who interact more frequently and deeply with QRM will require a commensurate level of training to ensure they can fulfill their responsibilities within the program. Table 7-1 provides a training model for the roles described in Chapter Nine.
Table 7-1: Role-based training model to enable risk maturity

<table>
<thead>
<tr>
<th>Role</th>
<th>Objective of training</th>
<th>Points to emphasize</th>
</tr>
</thead>
<tbody>
<tr>
<td>All employees</td>
<td>Provide an overview of QRM principles and practices</td>
<td>• QRM does not replace the obligation to follow cGMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk management is part of daily life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It is everyone’s responsibility to manage risks to the patient</td>
</tr>
<tr>
<td>Subject Matter Experts</td>
<td>Enable participation in QRM activities</td>
<td>• QRM is not surrogate for sound science</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• QRM requires the use of data and scientific knowledge to be effective</td>
</tr>
<tr>
<td>System or Process Owners</td>
<td>Ensure ownership and accountability for QRM</td>
<td>• Roles and responsibilities for QRM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Appropriate and inappropriate use of QRM</td>
</tr>
<tr>
<td>QRM Experts (Facilitators)</td>
<td>Build expertise in QRM</td>
<td>• Refer to section 7.3</td>
</tr>
<tr>
<td>Decision makers</td>
<td>Enable risk-based decision making</td>
<td>• QRM is an input into decision making; it is not the decision</td>
</tr>
<tr>
<td>Leadership</td>
<td>Secure a commitment to QRM</td>
<td>• The role of governance and culture in successful QRM (refer to Chapter Nine and section 7.4, respectively)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• The importance of leadership commitment in the success of QRM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• The value of QRM to the patient and the business</td>
</tr>
</tbody>
</table>

The role-based training described above should not be delivered only once; it is important to periodically refresh individuals on QRM principles and practices to ensure the knowledge remains current and easily accessible to the employee. Companies mature in QRM tend to perform annual re-trainings, either as standalone efforts or as part of other routine training such as cGMP refreshers. (128)

Developing organizational awareness of QRM principles and practices achieves several objectives that serve to enhance risk maturity. It gives employees the tools to identify, reduce, and communicate quality risks that might be present in their daily work. It enables a continuous
improvement mindset by giving employees the vocabulary and opportunity to speak up about quality risks and opportunities for improvement. (131) It helps overcome cultural inertia that may be present in historically reactive operational cultures. Finally, organization-wide familiarity with QRM ensures that all employees remain aware of their role in managing risk to the patient.

7.3 Building expertise in QRM

Many experts and authors espouse the need to build quality risk management expertise within the pharmaceutical and biopharmaceutical industries. These industries are founded in various sorts of expertise: expertise in patients’ medical needs, the clinical benefits of medicines, the science underpinning drug research and development, the manufacturing science required to produce these drugs, the quality system elements to ensure patient protection, and the regulatory science underpinning the manufacturer-regulator relationship. Despite this, there is a lack of deep understanding of the principles and practices of QRM: the very principles and practices that are being integrated throughout each of these areas. (125) (132) As stakeholders have evolved their appreciation of the benefits offered by QRM, each of these areas of expertise, once considered sufficient to deliver value to the patient, are now rendered vulnerable. Critical knowledge necessary to fulfill their role is lacking. The need for a deeper understanding of the ways in which QRM should be used to enable product realization and ongoing safety and efficacy is clear.

Some of the experts interviewed as part of the research made a distinction between training and education. (132) (132) Training, they noted, teaches people basic concepts required to fulfill their job responsibilities and execute tasks as intended. Education, on the other hand, provides a deeper perspective on the intent, principles, and practices associated with a given area to enable people to go further than what might be provided by training alone. It transfers knowledge and gives
students the skill set to synthesize this knowledge and create additional knowledge as they progress. Education, rather than training, is what is needed within industry for QRM. The researcher proposes that such an education program might apply three categories to each student, based on their level of progression through the program and demonstrated mastery of QRM principles and practices, as illustrated in Table 7-2.

Table 7-2: Education levels to develop QRM experts

<table>
<thead>
<tr>
<th>Level</th>
<th>Level of educator involvement</th>
<th>Level of structure</th>
<th>Focus of education</th>
<th>Educational premise</th>
<th>Skills gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidate</td>
<td>High</td>
<td>High</td>
<td>Course work, case study review</td>
<td>“learn by seeing”</td>
<td>Broad understanding of principles, tools, and application</td>
</tr>
<tr>
<td>Apprentice</td>
<td>Moderate</td>
<td>High</td>
<td>Use of skills under a seasoned QRM expert</td>
<td>“learn by doing”</td>
<td>Application of student skills in real-life settings, flexibility to “think outside the box”</td>
</tr>
<tr>
<td>Expert</td>
<td>Low</td>
<td>Low</td>
<td>Independent use of skills, mentorship of apprentices</td>
<td>“learn by teaching”</td>
<td>Refinement of expertise, knowledge transfer</td>
</tr>
</tbody>
</table>

At the Candidate level, the coursework progresses from a basic review of QRM regulation, terms, and tools through more complex concepts such as the development of risk control strategies, QRM facilitation skills, risk communication, and risk review, finally ending with advanced concepts such as human heuristics and bias and adaptation of QRM approaches to real-life scenarios. Table 7-3 summarizes recommended coursework during the Candidate level of QRM education, based largely on the research described in this thesis.

At the Apprentice level, the student is expected to apply knowledge gained during the Candidate coursework to real-life scenarios in a work setting, under the tutelage of a seasoned QRM expert.
Such apprenticeship may involve activities such as co-facilitation of risk assessments, participation in Community of Practice-type knowledge sharing forums, and exposure to senior leadership as risk-based decisions are discussed and taken. The apprenticeship program benefits from a high level of structure, with defined opportunities and mentor partners, to ensure the apprentice has an opportunity to exercise skills and be exposed to scenarios outside of their comfort levels. The apprenticeship program provides a way for students to learn on the job and experience success and failure in QRM endeavors without exposing the business and the patient to undue risk.
Table 7-3: Coursework for QRM Candidates

<table>
<thead>
<tr>
<th>Course</th>
<th>Included topics</th>
<th>Section references in this thesis</th>
</tr>
</thead>
</table>
| QRM Basics           | • ICH Q9  
• QRM standards: ISO 14971 and ISO 31000  
• QRM terms  
• 2.2.2  
• 6.2  
• 6.1                                                                                                                                               |                                   |
| QRM Applications     | • ICH Q8(R2) and ICH Q11  
• ICH Q10                                                                                                                                         | • 2.2.3  
• 2.2.4  
• 8.3                                                                                                                                              |
| QRM Tools            | • Failure Modes and Effects Analysis (FMEA)  
• Hazard Analysis and Critical Control Points (HACCP)  
• Preliminary Hazard Analysis (PHA)  
• Bowtie Analysis: Fault Tree Analysis (FTA) and Event Tree Analysis (ETA)  
• Risk-based Impact Assessment (RBIA)  
• 8.2.2                                                                                                                                           |                                   |
| QRM Initiation       | • Developing the risk question  
• Risk tool selection  
• Building a risk team  
• Preparing for a risk assessment                                                                                                                 | • 8.2                                                                                     |
| Risk Control         | • Risk control methods  
• Identifying GMP controls  
• Risk control option analysis  
• 6.2.2  
• 6.4  
• 8.48.4                                                                                                                                          |
| Risk Review          | • Risk review timing and objectives  
• Data sources  
• Making sense of the data                                                                                                                      | • 8.5                                                                                     |
| Risk Communication   | • Identifying stakeholders  
• Communication methods  
• What should be communicated  
• 6.4.1  
• 8.6                                                                                                                                              |
| Facilitation skills  | • Situational leadership  
• Managing conflict  
• Leading meetings  
• Heuristics and biases  
• None  
• 48 With the exception of heuristics and biases, facilitation skills are not specific to QRM and are therefore not discussed in this thesis. Heuristics and biases did not warrant significant discussion based on the research question, however are critical knowledge for the QRM Candidate. See, for example, (63), (64), (157), (222). |
Students at the Expert level⁴⁹ focus on using their mastery of QRM for the benefit of the patients they and their organizations serve. In addition, they nurture the next generation of QRM Experts as coaches and mentors. The process of mentoring brings with it an additional level of learning, as students with new knowledge, ideas, and mindsets challenge the mentor.

Companies with mature QRM programs invest heavily in building this level of QRM expertise. (130) This investment offers a significant return, of course, in the form of core knowledge that can be applied throughout the quality system and over the entire product lifecycle. The people working with and through QRM are assets to be invested in and championed; developing core expertise in QRM principles and practices enables companies to better manage risk to the patient.

7.4 Risk culture

Several experts who participated in the Phase 3 research cited a company’s culture with respect to QRM as the aspect most predictive of success, and also of failure, in managing risk to the patient. Cultural influences have made or broken risk management in other industries as well, as in the culture of complacency and the normalization of deviance seen at NASA (discussed in Chapter 6) and the failure to implement appropriate design controls in the 1970s model Pinto at Ford that is common attributed to the unethical prioritization of profits over people.⁵⁰ (133)

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⁴⁹ Indeed, even experts should be considered students of QRM, as the consistent evolution of the practice necessarily entails an ongoing commitment to learning.

⁵⁰ The Ford Pinto debacle is commonly studied by business ethicists and risk management practitioners alike. The 1970s model Pinto had a serious design flaw; the fuel tank was positioned in a way that made it vulnerable to explosion upon impact, and also made it difficult or impossible for the vehicle occupants to subsequently escape the fiery crash. Pinto designers admitted to keeping this information from the CEO at the time, since safety was not a priority at the company. Cost and time, however, were. Once the Pinto went to market and drivers began to suffer as a result of the design issue, the company still chose to continue selling the vehicle. Ostensibly the justification was that a mass recall and part replacement was more expensive than the expected legal settlements in wrongful death tort suits. (141) The company culture at Ford serves as a cautionary tale for any QRM practitioner.
The Phase 2 research identified fear as an obstacle that is currently preventing progression towards more mature QRM in the pharmaceutical and biopharmaceutical industries. Other experts cited a lack of interest in exploring uncertainty as a hallmark of an immature risk culture, while others cited reactive, “fire-fighting” cultures that reward problem solving instead of problem prevention. (134) (132) (127) The lack of a common risk vocabulary, and the willingness to use it, is another indicator of weak risk maturity, as is the feeling that QRM adds value only so far as the regulations require it. (129) (135) In immature risk cultures, personnel are loath to participate in QRM activities, often actively avoiding them. (128)

These immature risk cultures may be relics of older regulatory paradigms, predating ICH Q8, Q9, Q10, and Q11. The semi-structured expert interviews and philosophical dialogues held in the Phase 3 research indicated that there may be lingering fear of risk, drawn off the impression that regulators, in particular, would historically not tolerate quality risk of any sort. (127) (128) Mohachkar et al reflect that “the industry [has] too long been regulated into a culture in which a static process [is] the only safe process.” (136) Indeed, as discussed in Chapter Two, pharmaceutical and biopharmaceutical regulation has been historically rule-based, rather than risk-based. Compliance was king, and there was an assumption that perfect compliance would result in perfect quality. Some companies, low in risk maturity, may still cling to this older paradigm as the way it has always been done.

The unfortunate fact is that in the pharmaceutical and biopharmaceutical industries, culture change often follows regulatory sanctions, such as an import alert, warning letter, consent decree, or revocation of a GMP certificate—all situations that represent grave quality problems and associated risks to the patient. The challenge becomes how to identify ways to change culture
proactively. Juan Andres, head of quality at Novartis, positions it as an issue for leadership: “We need to be able to articulate and to be able to catalyze that mindset and that cultural change in our organizations with the business leaders prior to punished, or punishing the patients…” (137)[emphasis added] The challenges in achieving momentum with a new organizational mindset were summarized by Richard Bowles, head of quality at Schering-Plough, who discussed the evolving levels of commitment as cultural change takes hold. (137) Table 7-4 summarizes these levels of commitment.

<table>
<thead>
<tr>
<th>Level of commitment</th>
<th>Mindset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denial</td>
<td>“I will do it if I have to.”</td>
</tr>
<tr>
<td>Resistance</td>
<td>“I will obey the rules.”</td>
</tr>
<tr>
<td>Exploration</td>
<td>“I will support the effort.”</td>
</tr>
<tr>
<td>Commitment</td>
<td>“I stand for this.”</td>
</tr>
</tbody>
</table>

Table 7-4: Levels of commitment in cultural change

There are ways to accelerate the organization through these levels of commitment, steepening the learning curve associated with understanding and adopting new ways of thinking—as QRM surely entails. A first step is to develop organizational awareness of QRM, as discussed earlier in this chapter. Some large pharmaceutical and biopharmaceutical coupled the initial role-based training efforts with company-wide “QRM Days”, engaging personnel with QRM-themed games, “lunch and learn” talks about QRM topics from all levels of the organization, and QRM poster sessions. One site achieved quick success in permeating the organization with a QRM mindset through their “12 Days of Riskmas” event, using holiday themes to introduce and reinforce QRM topics throughout their site. (128) Events such as these can diffuse some of the fear associated with risk identification and management, and can allow personnel to engage with leadership and decision makers who reinforce their commitment to a risk-savvy culture.
Other firms have “branded” QRM through the design of risk management slogans and logos. The branding is then used on multiple forms of communication—email signatures, presentation slides, reports, and posters around the facility—to remind personnel of QRM. (138) (130) Uydess and Meyers describe such branding as a key element of a successful cultural transformation, noting “To help drive and sustain [cultural] changes, a compelling… message must be developed—in effect, internally branding the effort. The message must be clear, relevant, understood by all, and designed to provide a point around which every employee can rally, motivating them to contribute to the effort.” (139) This effort should also work to reverse any preconceptions that risk management is “the brakes of the operation more so than valued partners.” (140)

In addition, crafting a reward and recognition program for personnel who exhibit anticipatory and avoidant behaviors will encourage others to follow and demonstrate the organization’s commitment to the new risk culture. (132) (127) This is particularly important within organizations that have historically rewarded reactive behaviors, as these organizations have reinforced the perception that problem-solvers are valued, while risk managers go unnoticed. Vesper shared an anecdote to demonstrate the point:

“I was working with a biopharma company and they prided themselves as fire-fighters. If something went wrong, they would work twenty hours a day and over weekends to fix it, and once they did they would get their picture taken with the site director and it would be put on their interval website or newsletter. They were rewarding fire-fighters. And what was so hard about this firm, is that QRM is proactive. And they weren’t rewarding proactive behaviors, or avoiding a problem instead of solving it.” (127)
Reward and recognition programs to reinforce proactive behaviors can vary from formal to informal in line with typical company policies, however it should be similar in measure to the programs used for reactive behaviors—those with a QRM mindset should get equal or greater symbols of appreciation as those who capitalize off the failure of QRM.

For those firms ready to transition to the modern quality archetype of risk-based quality and compliance have a clear idea of what maturity looks like. Pat Barrett, Auditor-General for Australia, listed ten attributes of mature risk cultures (positioned as KPIs for risk management):

1. Integrated risk management approach: an organization in which risk management is forward-looking and integral to all business processes
2. Committed and led: an organization with a strong leadership commitment to risk management at the highest levels
3. Positive and proactive focus: an organization that seeks to identify and manage risks before they manifest, rather than after
4. Process-driven: an organization with a framework capable of executing risk management processes
5. Planned for continuous improvement: an organization with a clearly defined risk planning process and ongoing monitoring and review
6. Audited and documented: an organization that confirms its application of risk management principles and processes
7. Active communication: an organization with a defined risk communication plan, that communicates risks actively to internal and external stakeholders
8. Resourced: an organization that has committed adequate resources, both financial, time, and personnel, to the management of risks
9. Trained and Educated: an organization that is committed to training and education of staff in risk management principles and is willing to fund such education
10. Value-based decisions: an organization that makes business decisions based on risk assessment outcomes (141)

Mature risk cultures are composed of people with an innate curiosity and drive to better understand and manage risks. (134) (126) These are open, transparent cultures that have not assigned an inherently negative value judgement to risks; risks and their management are seen not as mandatory compliance element but as opportunities to improve the business and better protect the patient. (134) (132) (142) (130) (125) In mature risk cultures, there is eagerness to employ QRM principles and practices since the benefits of doing so are clear to all. People actively champion QRM; that is, until the highest level of maturity is reached where QRM is so fully integrated into everyday work that the use of risk management concepts no longer requires conscious effort. Of course, a strong risk culture is one that is proactive, anticipatory, and risk avoidant; it is a culture that puts patient protection first.

This chapter outlined an ideal state of QRM with regard to the people working within it, including role-based training and awareness, the process and benefits of nurturing QRM experts, and the role of risk culture. Chapter Eight will characterize maturity for the QRM process to be used by these QRM practitioners, aimed at shifting the focus from “doing QRM” to “managing risk to the patient.”
Chapter Eight: What QRM Maturity Looks Like - Process

This chapter seeks to characterize risk maturity with regard to the process—the activities that comprise the QRM lifecycle. This chapter begins with the introduction of a concept intended to serve as the guiding light for subsequent quality risk management efforts, the living risk assessment library. This library focuses the organization on holistically managing aspects of that directly relate to the patient, minimizing the emphasis on performing QRM activities for less important aspects. It is, in a sense, the principle of risk management applied to risk management itself. The sections that follow characterize what maturity looks like over the QRM lifecycle, and proceed in rank order of QRM initiation, risk assessment, risk control, risk review, and risk communication. Finally, an alternative QRM lifecycle is proposed, based upon the more effective QRM process proposed in earlier sections.

8.1 Constructing a holistic risk assessment library

ICH Q9 does not distinguish between two complementary but distinct concepts: quality risk management and risk-based decision making. This difference is more effectively communicated in ICH Q10, which distinguishes between the product lifecycle and the quality system working within that lifecycle. The QRM lifecycle proposed by ICH Q9 implies that risk management activities necessarily entail each of the process steps to a greater or lesser extent; there is no acknowledgement that QRM principles may be applied, in the absence of the complete QRM lifecycle, throughout the quality system. Industries such as aerospace (discussed in Chapter Six) and companies with mature QRM programs distinguish between these two applications of QRM and have structured their programs appropriately. (109) (129) (134) (128)
An operational definition for risk-based decision making for the pharmaceutical and biopharmaceutical industries might be “the use of the principles of quality management risk outside of the lifecycle framework to assist with quality-related decision making.” For example, one might apply QRM to help determine a commensurate depth of investigation for a process deviation or complaint, or to evaluate the appropriate frequency for preventive maintenance, calibration, or self-inspection. These applications of QRM do not necessarily require the totality of the lifecycle to be followed; rather, a risk assessment or risk-based approach may be conducted to facilitate a decision without continuing into the risk reduction, risk acceptance, and risk review portions of the lifecycle. It is therefore necessary for firms to distinguish between living risk assessments, which follow the full breath of the QRM lifecycle, and ad hoc risk assessments, which may only address a portion or portions of the lifecycle, depending on the risk question. This alleviates some of the administration burden of a QRM program by focusing energy and resources (particularly within risk review) on the applicable portions of the lifecycle.

Living risk assessments should represent the core of the QRM program. These are performed on a product, process, or system, with the objectives of understanding the associated risks, controlling them to an acceptable level, and reviewing the risks in light of changing conditions to evaluate the continued relevance of the identified risks and the continued effectiveness of risk controls. On the other hand, ad hoc risk assessments are likely to be performed as part of an integrated quality system, to make decisions within specific contexts. These risk assessments need not be subject to risk review, but are often the input into the review of living risk assessments. Many companies struggle as they attempt to review risk assessments intended for risk-based decision making rather the QRM lifecycle, since related decisions have been taken and resultant next steps enacted. A mature QRM program addresses and embraces both of these types of risk assessments.
It follows, of course, that the products manufactured by a firm should be subject to the full rigors of the QRM lifecycle, and therefore have living risk assessments associated with them. These represent the most direct link to the patient and should be continually evaluated in a QRM framework throughout their lifecycle. (143) The question then becomes, what living risk assessments are necessary to ensure that risks to the patient are fully understood and controlled?

As discussed in the Viracept story in Chapter One, many firms have approached this by creating thousands of risk assessments, each covering a small segment of the total knowledge required to truly manage risks to the patient. Schmitt notes that in his experience working with numerous pharmaceutical and biopharmaceutical companies, “… one is left with hundreds (sometimes thousands) of risk assessments all over the place, not linked to a plan or a process, just floating.” (135) At companies with less mature QRM programs, risk assessments, and therefore the QRM lifecycle, are initiated as the need arises, and are seldom planned in advance to fit within an overarching strategy to achieve full risk understanding. (135) (144) This approach soon proves its folly, as the forest is lost for the trees and a complete picture of the risks to which the patient might be exposed are not fully understood. Further, the administrative burden posed by the need to perform risk review activities on thousands of individual risk assessments soon becomes unmanageable, causing an increased focus on “doing QRM” at the expense of managing risk to the patient.

A mature QRM program would have a clear picture of the minimum scope required to achieve holistic risk knowledge and would have established a QRM plan to achieve this. For example, a firm may elect to use the approach commonly employed by medical devices, with one risk assessment (and QRM lifecycle initiation) each for the product, process, and use. However,
discomfort with this sparse approach is often voiced by various departments: what about the risks associated with the manufacturing facility? The utilities within the facility? The equipment used to run the manufacturing process? The computer systems used to run those equipment? And once again the firm moves to the other side of the pendulum, with an excess of risk assessments of small scope ruling the day. (128) (138) A more streamlined and comprehensive approach is to evaluate the parts that comprise the whole and proactively design a holistic living risk assessment library. Such a living risk assessment library might leverage platform processes and technologies and similarities in design and construction to cover the totality of product considerations, as shown in Table 8-1.

Using the living risk assessment library model, risk identification would occur within the context of a pre-planned risk assessment, rather than before. Therefore, individual efforts to perform risk assessments for pre-defined risks, such as cross-contamination, integrity of the supply chain/value stream, or the level of cGMP required of excipient manufacturers, would no longer be necessary; these would already be addressed in the applicable living risk assessment. In this way the living risk assessment library model enables a more streamlined yet comprehensive approach such that all applicable risks are identified within the context of a holistic risk assessment.

In order to maximize the effectiveness of the living assessment risk library concept, the organization must be aware that these must be kept living; that is, a new living risk assessment should only be created if a gap is discovered within the library construct. Rather, the risk assessments that already compose the library should be revisited, revised, expanded, or contracted based changes that may occur to the topic that was assessed, in accordance with the principles of risk review.
Table 8-1: Example of an optimized living risk assessment library

<table>
<thead>
<tr>
<th>Focus of risk assessment</th>
<th>Includes components of…</th>
<th>Delivers knowledge related to…</th>
</tr>
</thead>
</table>
| **Manufacturing process** | • Manufacturing equipment  
• Automation  
• Equipment cleaning and sterilization | • Design and content of master batch production records  
• Process and operational control strategies  
• Process monitoring strategies  
• Product sampling and testing plans  
• Cleaning process design and validation  
• Computer systems design and validation  
• Maintenance and calibration plans  
• Inspection plans and acceptance levels |
| **Facility** | • HVAC systems  
• Critical utilities (e.g. water, steam, and process gases)  
• Facility flows (e.g. personnel, product, waste) | • Contamination and cross-contamination control strategies  
• Cleanroom capabilities and classification  
• Environmental monitoring plans  
• Critical utilities monitoring plans |
| **Starting/raw materials and components** | • Material quality and safety  
• Extractable and leachable profiles | • Product impurity profiles  
• Supplier qualification  
• Supplier management  
• Component lifecycle management |
| **Analytical methods** | • Method capability and repeatability  
• Laboratory instruments  
• Analyst interface  
• Data capture and trending systems (e.g. Laboratory Information Management Systems) | • Data integrity  
• Analytical method design and qualification  
• Computer systems design and validation |
| **Product shipping** | • Shipping lanes  
• Stability requirements  
• Temperature requirements  
• Handling requirements  
• Import/export considerations | • Counterfeiting, tampering, and diversion prevention and response plans  
• Shipping configuration design and qualification  
• Cold chain requirements  
• Supplier qualification  
• Supplier management  
• Good distribution practices |
8.2 QRM initiation

In many companies, the QRM process is initiated informally, without any minimum requirements that would prove critical to the success of the effort; in some cases there is no communication that QRM has been invoked until after a risk assessment is complete. These practices could lead to false-starts and other problems, such as weak, unclear or conflicting objectives, inadequate expertise on the risk team, selection of a sub-optimal risk tool, or redundant or vague scope of the QRM effort. Companies with mature QRM programs tend to pre-plan QRM efforts, as discussed in the context of the QRM Plan in Chapter Nine, and apply a structured approach to the initiation process to provide an appropriate level of oversight and direction for the activities to follow. A mature QRM initiation process would require the initiator to define the risk question or objective, select an appropriate risk tool, and identify the expertise and data needed and individuals possessing that expertise and knowledge, and ensure that the QRM effort is aligned with the overall QRM strategy. Depending on the level of risk maturity of the organization, a defined QRM initiation process may also include requirements to ensure the proper ownership, select a qualified facilitator, prepare for the risk assessment, and understand the resources available to control any resultant risks. The QRM initiation process should be considered a planning step critical to the success of the effort, and should entail a commensurate level of structure and energy. Appendix I offers a template that can be used by pharmaceutical and biopharmaceutical companies to enhance their maturity in QRM initiation.

51 In companies with very mature QRM programs, QRM would be seamless within the organization and therefore initiation of QRM would not require a formal process or associated communication effort. However, as discussed in Chapter Five, most pharmaceutical and biopharmaceutical companies have not yet reached this level of maturity and should follow a structured approach to QRM initiation until such time as control and oversight over this phase of the lifecycle is no longer necessary.
8.2.1 The risk question

Though ICH Q9 mentions it only in passing, perhaps the most important deliverable from QRM initiation is the definition and documentation of the risk question. The risk question is that which the risk assessment seeks to answer. It encompasses the problem statement in a question format, serving as a compass for the activities to come. Broad risk assessments, such as those used to construct the living risk assessment library discussed earlier in this chapter, tend to use short and simple risk questions, such as “what are the risks associated with this process?” Narrowly-scoped, specific risk assessments tend to employ more complex risk questions, such as “what are the risks of exceeding the storage temperature during transport of this product by air freight from Ireland to Hong Kong in February?” (61)

Some companies forgo a risk question and instead document the objective of the risk assessment. The researcher cautions against this practice for several reasons: an objective may encourage incorrect use of QRM by implying a foregone conclusion, such as a decision that has already been made or a justification of an inappropriate practice (as in “The objective of this risk assessment is to justify a reduced level of training for aseptic processing operators.”) and may also introduce bias into the QRM exercise through the assumption that the objective is appropriate. The use of a risk question has several advantages over an objective in QRM, including:

- Minimizing bias by positioning the QRM exercise as one of learning, rather than assertion, which in turn means there are no “right” or “wrong” answers
- Allows the data to speak for itself in the context of a risk assessment, rather than to support a pre-defined goal
- Allows for uncertainty to be present and acknowledged
This is not to say that the use of risk questions always represents a greater level of risk maturity. Weak risk questions may exhibit characteristics similar to an objective, as in “what is the risk of not doing <activity>?”. Conversely, strong risk questions will be agnostic to the outcome.

Table 8-2 illustrates how varying levels of risk maturity might manifest during this step of QRM initiation.

<table>
<thead>
<tr>
<th>QRM Topic</th>
<th>Least mature</th>
<th>More mature</th>
<th>Most mature</th>
</tr>
</thead>
<tbody>
<tr>
<td>For environmental monitoring</td>
<td>“The objective of this risk assessment is to justify a reduction in sampling locations and frequency for the environmental monitoring program.”</td>
<td>“What are the risks of removing sampling locations and reducing the frequency of sampling in the environmental monitoring program?”</td>
<td>“What sampling locations and frequency should be employed in the environmental monitoring program, based on the risk?”</td>
</tr>
<tr>
<td>For deviations</td>
<td>“The objective of this risk assessment is to justify the release of product implicated in deviation X.”</td>
<td>“The objective of this risk assessment is to determine whether product implicated in deviation X should be released.”</td>
<td>“Given that deviation X occurred, what are the risks to product quality and patient safety?”</td>
</tr>
<tr>
<td>For change management</td>
<td>“This risk assessment was performed to satisfy the QRM requirement in the Change Management procedure.”</td>
<td>“This risk assessment was performed to determine the risks associated with the proposed change and reduce them to an acceptable level.”</td>
<td>“Should the proposed change proceed based on the risks? If so, what effect does this change pose on the risk profile of the associated process?”</td>
</tr>
</tbody>
</table>

8.2.2 QRM tool selection

Two-thirds of the experts interviewed for the Phase 3 research noted that a mature QRM program would have an extensive risk “toolkit” that can be used to support the QRM lifecycle. (129) (134)
Risk tools support the conduct of risk assessments, including elements of risk identification and risk analysis, at a minimum. A variety of risk tools are listed in ICH Q9, including:

- Flowcharts
- Check sheets
- Process maps
- Ishikawa diagrams (also known as fishbone or cause and effect diagrams)
- Failure Modes and Effects Analysis (FMEA)
- Failure Modes, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk Ranking and Filtering (RRF)
- Supporting statistical tools, such as control charts, histograms, and process capability analyses

Despite this, many companies less mature in QRM application tend to use a single tool. By far the most common tool in use the pharmaceutical and biopharmaceutical industries is FMEA, a fact lamented by QRM experts. While FMEA has its place in any QRM toolkit, the rigidity of the tool construct poses challenges when used for risk questions that are ill-fit for the tool design. For example, the identification of failure modes, causes, and effects inherent in FMEA is useful when trying to optimize a process to minimize risk, however is
of little value when trying to understand the impact of an event on product quality and patient safety for which the underlying cause may be of minimal relevance.

A robust toolkit enables QRM practitioners to select the best-fit approach for the risk question at hand and empowers organizations to fully avail themselves of different levels of formality inherent in each tool. As mentioned in section 2.2.2, ICH Q9 advises that “the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.” (45) FMEA is generally recognized as a formal risk tool; the over-use (and therefore misuse) of FMEA means that less mature QRM programs do not apply this principle of proportionate formality and effort. Vesper and O’Donnell listed “using formal QRM on everything” as a major trend and misapplication of QRM seen across industry. (145) Darrel Morrow, Senior Director of Quality Systems at Acceleron Pharma, reiterates that “it cannot be stressed enough that good systems use simple tools and avoid complexity. In this industry, it is easy for scientists to become hung up on ensuring accuracy; that means that people often add details and specifics to risks that do not actually help create a meaningful risk assessment.” (142)

Several sources note that formality is not a binary concept in QRM; rather, it is a “spectrum” ranging from informal to very formal, with each risk tool having its place along the spectrum. (62) (126) It is this researcher’s opinion that the formality spectrum described by these sources has minimal utility in a practical sense, since the distinction between risk tools is less a matter for formality than it is of conceptual design and intended application. Companies seeking to enhance their level of risk maturity would benefit most from acknowledging the difference between formal and less formal risk tools, and then developing risk toolkits to include a small selection of both types. A recommended minimum toolkit is offered in Table 8-3.
Table 8-3: Recommended minimum risk tools to increase risk maturity

<table>
<thead>
<tr>
<th>Tool</th>
<th>Formality</th>
<th>Optimized for…</th>
<th>Enables delivery of…</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMEA</td>
<td>Formal</td>
<td>Product, process, and system optimization and continuous improvement</td>
<td>Process control strategies</td>
</tr>
<tr>
<td>HACCP</td>
<td>Formal</td>
<td>Facility and utility optimization and continuous improvement</td>
<td>Monitoring plans</td>
</tr>
<tr>
<td>Risk-based Impact Assessment (RBIA)</td>
<td>Formal</td>
<td>Impact assessments</td>
<td>Risk-based decision making</td>
</tr>
<tr>
<td>Risk Estimation Matrix (REM; sometimes called a simple hazard analysis)</td>
<td>Less Formal</td>
<td>Frequent use in a variety of circumstances</td>
<td>Resource and project prioritization, Identification of areas that may require analysis through more formal tools</td>
</tr>
<tr>
<td>Risk Ranking and Filtering</td>
<td>Less Formal</td>
<td>Customization</td>
<td>Integration of QRM principles into the quality system</td>
</tr>
<tr>
<td>Decision trees and Ishikawa diagrams</td>
<td>Less Formal</td>
<td>Customization</td>
<td>Integration of QRM principles into the quality system, Risk-based decision making</td>
</tr>
<tr>
<td>Check sheets</td>
<td>Less Formal</td>
<td>Risk identification</td>
<td>List of applicable risks from a pre-identified set</td>
</tr>
<tr>
<td>Ishikawa diagrams</td>
<td>Less Formal</td>
<td>Risk identification</td>
<td>List of causal factors</td>
</tr>
</tbody>
</table>

Once an appropriate toolkit has been defined, the most challenging aspect of QRM initiation begins-- selecting the most appropriate risk tool. Murray and Reich explain the challenge as follows:

“Successful QRM tool selection begins with an awareness of the interrelationship between risk understanding and the choice of QRM tools. Knowledge pertaining to potential risks both influences, and is influenced by, the selection of QRM tools… This interrelationship may seem paradoxical; QRM tools are typically used to facilitate and organization risk
identification, yet it is premature to select a QRM tool without knowing the nature of the risks to be assessed.” (146)

This paradox can be overcome through a deep understanding of the capabilities and limitations of individual risk tool, combined with an evaluation of the risk question at hand. Murray and Reich compare and contrast the characteristics of some common risk tools in a matrix format, as shown in Figure 8-A. While this comparison is valuable, it does not acknowledge the level of formality required of the assessment, nor is the risk question taken into account. This researcher, using learnings from Murray and Reich, philosophical dialogues, expert interviews, and work experience has addressed these shortcomings through the development of a decision tree to facilitate risk tool selection in mature QRM programs, as shown in Figure 8-B.
<table>
<thead>
<tr>
<th>Considerations</th>
<th>FMEA</th>
<th>FTA</th>
<th>Fishbone/Ishikawa</th>
<th>HACCP</th>
<th>HAZOP</th>
<th>PHA</th>
<th>RR&amp;F</th>
</tr>
</thead>
<tbody>
<tr>
<td>If process/product/system knowledge is limited (ex: early lifecycle phases)</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>✓,2</td>
<td>✓</td>
<td>✓,2</td>
</tr>
<tr>
<td>If process/product/system knowledge is advanced (ex: later lifecycle phases)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>If problem statement is simple or if an elegant assessment is appropriate</td>
<td>✓,2</td>
<td>✓</td>
<td>✓</td>
<td>✓,2</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>If problem statement is highly complex or if a detailed assessment is required</td>
<td>✓,1</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>✓,1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>If risk ranking is desired</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>If risk detection capability is limited</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>If risk data is more qualitative in nature</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓,2</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>If risk data is more quantitative in nature</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>If demonstration of the effectiveness of risk controls is required</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>If risk identification is a challenge, if hidden risks need to be revealed, or</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>if structured brainstorming is desired</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

✓ Tool is likely a suitable fit under this consideration and is designed or capable to perform this way.
X Tool may have less (or no) capability to deliver under this consideration or may be either overly complicated or too simplistic for the task.
! Tool may be suitable, however effectiveness may be limited due to challenges in rating some probabilities of occurrence. It may be challenging to rate risk probabilities if there is limited means to detect those risks in the first place.
1 Brainstorming capability of this tool may be particularly beneficial for this type of assessment.
2 Capabilities of this tool can be scaled back to accommodate qualitative or more simple assessments.

Figure 8-A: Murray and Reich’s comparison of common risk tools (146)
Figure 8-B: Decision tree to aid in risk tool selection
8.2.3 QRM team selection

With over a decade of experience in the pharmaceutical, biopharmaceutical, and medical device industries, this researcher has become a strong proponent of the use of multidisciplinary teams to solve problems. Ideas and intelligence are cumulative, and having the best and brightest work together on a topic almost always leads to a better outcome. ICH Q9 acknowledges the importance of using a team approach to QRM, stating “Quality risk management activities are usually… undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas… in addition to individuals who are knowledgeable about the quality risk management process.” (45) A critical component of the QRM initiation process includes the identification of the QRM team and chartering its membership.

Companies less mature in QRM tend to struggle with the idea of expert teams. McFarland describes her least mature clients as “those that do not require cross-functional team involvement in risk exercises.” (134) In addition, many firms confuse functional group affiliation with expertise; for example, working within the quality control microbiology laboratory at a pharmaceutical firm does not necessarily render one an expert microbiologist. (128) Companies mature in QRM do not seek to ensure departments are represented in a risk assessment; rather, they aim to have all necessary scientific expertise at the table when QRM is initiated.

The term “subject matter experts”, or SMEs, is typically used to identify these individuals. A subject matter expert might be defined as one who has both access to scientific data and the knowledge to interpret that data through the lens of risk. This expertise tends to be in a scientific or engineering discipline of course, and should entail an appropriate level of education, experience,
and ongoing learning to ensure the expert’s reference point is not solely academic nor industrial, and is kept in tune with scientific advancements over time. These experts, comprising the bulk of the QRM team, need only possess a superficial knowledge of QRM tools in order to fulfill their role on the team. Under the guidance and tutelage of a qualified risk facilitator, their expertise can be translated into a QRM framework to create deliverables.

At QRM initiation, the necessary data and expertise should be identified before membership on the QRM team is selected. This ensures that individuals are not asked to participate based on functional group affiliation or availability, but instead based on their knowledge and the relevance of that knowledge to the topic under evaluation. Appendix I provides a template for QRM initiation that guides the user through this essential process.

8.3 Maturity with regard to risk assessment

There is a wealth of literature available on risk assessments—books and articles describing risk tools, methods, considerations, and “best practices” abound. The gap in this literature, as discussed in Chapters One and Two, is a discussion about how to use risk assessment to better manage risk to the patient. The researcher has therefore chosen to approach this section, focused on maturity of risk assessment, not on those tips already socialized throughout the pharmaceutical and biopharmaceutical industries, but rather on how to best execute living risk assessments to ensure patient protection. The living risk assessment execution strategy described in this section was initially proposed and authored by the researcher as part of her work with the PDA QRM Task Force, and has since been published in the resultant technical report Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems. (147) For reference throughout this section, the approach will be referred to as SmartRA.
8.3.1 Hierarchies and QbD and failure chains, oh my!

Stephen Covey offered some wisdom that should be held sacrosanct when performing QRM: “begin with the end in mind.” (148) The “end” for pharmaceutical and biopharmaceutical companies is, of course, is the end user—the patient. All activities undertaken by drug manufacturing firms ultimately link to the patient, as shown in Figure 8-C. The patient crowns the pharmaceutical manufacturing hierarchy, and is supported by the medicinal product. The product, in turn, is realized through the manufacturing process, which is possible through the use of manufacturing systems, equipment, and technology. These are comprised of individual components—the constituent parts of the production and support systems. In order to protect the patient by assuring the safety and efficacy of the drug product, each of the layers in this hierarchy must be fully understood and carefully controlled.
Visualized a different way in Figure 8-D, the product is enabled by the process, with is enabled by systems, which are enabled by components. When the underlying hierarchy is well characterized, even a simple valve or gasket can be linked to patient protection.

Figure 8-D: Enabling chain of pharmaceutical manufacturing

As discussed in Chapter Two, ICH Q8(R2) describes the Quality by Design process and introduces specific vocabulary to describe the linkages between patient, product, and process. The aspects of a medicinal product that are critical to ensuring product efficacy and patient safety are called Critical Quality Attributes, or CQAs. (49) Examples of CQAs include potency, concentration or dose, sterility, and the presence of impurities in the product. CQAs are identified through product development data and preclinical and clinical evidence, illustrating how variation in a given quality attribute affects patient outcomes and product quality. Companies mature in QRM often employ a risk-based approach to CQA determination, using a risk tool that measures the strength of impact of the quality attribute on the patient and the uncertainty associated with that impact. Only those quality attributes that have strong scientific data supporting a lack of patient impact can be ruled out as CQAs. In the event there is insufficient evidence to support a claim that a given quality attribute will not affect the patient, the attributes will be considered a CQA to ensure it is adequately controlled. (103) CQAs therefore make a link between the product and the patient, as shown in Figure 8-E.
Once the CQAs for the medicinal product have been identified, the manufacturing process can be similarly evaluated. The process parameters that are critical to ensure CQAs are met are deemed Critical Process Parameters, or CPPs. These are identified during process development, using experimental data (such as Design of Experiment or DoE) and risk-based impact assessments. Only those process parameters that exhibit a strong correlation with, or causal link with, CQAs are deemed critical. As a result, CPPs link the process with the medicinal product in the pharmaceutical manufacturing hierarchy.

The CPPs are, in turn, controlled by manufacturing systems, including facilities, utilities, and production equipment. The elements of these systems that are critical to ensuring the CPPs are adequately controlled and monitored are deemed Critical Aspects, or CAs. Finally, the CAs require various components functioning in specific, reliable ways in order to be adequately controlled.
controlled; these components are referred to as Critical Aspect Design Elements, or CADEs. The term “critical elements” is used throughout the remainder of this section to refer to CQAs, CPPs, CAs, and CADEs as a group.

When viewed through the lens of QRM, the enabling chain of pharmaceutical manufacturing (shown in Figure 8-D) becomes a failure chain. Because of the relationship between each critical element, the failure of an upstream element necessarily can cause downstream elements to fail, as illustrated in Figure 8-F. For example, if an impeller fails (CADE), the mixer will fail (CA). This will lead to the mix speed or time being less than the process requires (CPP), which in turn could affect the homogeneity of the applicable solution being mixed (CQA).

![Critical element failure chain in pharmaceutical manufacturing](image)

The totality of the linkages between various levels of the pharmaceutical manufacturing hierarchy and the associated controls for the critical element failure chain are captured in what ICH Q8(R2)

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52 ICH Q8(R2) does not extend to a discussion of manufacturing systems or the associated CAs or CADEs. The term “critical aspect” in this context originates from ASTM E2500, Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment. (50) The term “critical aspect design element” was coined by the researcher for the purpose of continuing the pharmaceutical manufacturing lifecycle to its most basic element, the component level. This term has been defined and published within the PDA Technical Report No. 54-5, which the researcher authored in part. (146)
calls a control strategy—“a planned set of controls, derived from current product and process understanding that ensure process performance and product quality.” (49) Through implementation of the control strategy, a given stakeholder can focus on the level of the hierarchy that suits their job function (such as engineers for manufacturing systems, manufacturing personnel for manufacturing processes, and quality control personnel for product attributes), all the while ensuring that the patient needs are met. The structure of the product-process-systems interface as described in ICH Q8(R2), therefore, enables the first principle of ICH Q9 (i.e. “…The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient;”) to be applied in a clear and accessible way. (45) In a mature QRM program, the fundamental concept of the critical element failure chain and the applicable control strategy is derived from (or captured in53) each living risk assessment; this ensures that elements critical to product quality and patient safety are given a level of attention proportionate to their importance.

8.3.2 Developing a living risk assessment to ensure patient protection

The development of failure chains could, alone, serve as a robust living risk assessment to identify critical elements, calculate the risk, and develop controls. However, in order to illustrate the application of the living risk assessment model through a traditional risk tool, the risk tool decision

53 The researcher acknowledges that the approach described in this section varies slightly depending on the product lifecycle phase in which it is applied. For example, “legacy” products and processes in the commercial manufacturing stage of the product lifecycle may not have been created using a Quality by Design approach, and may have been characterized for criticality post hoc. In these instances, the approach to risk assessment maturity will leverage pre-defined critical elements. Products and processes in the development phase, however, can use the same approach to identify critical elements. This section and the examples that follow describe the application of this model for new products, but is equally applicable to legacy ones.
tree located in Appendix I was used and FMEA was selected as the best-fit risk tool. A brief primer on FMEA is warranted, before more sophisticated concepts are introduced.54

The risk identification step of an FMEA involves the identification of three components of risk: failure mode, failure cause, and failure effect. A failure mode can be defined as the manner in which an item could fail to meet its requirements. The consequence of a failure mode is termed a failure effect, while the reason for the failure mode is called a failure cause. In FMEA, there is no direct relationship between failure cause and failure effect; the failure mode intervenes between the two, as illustrated in Figure 8-G.

Figure 8-G: Relationship between failure mode, failure cause, and failure effect in FMEA

Once risk identification is complete and all failure modes and related causes and effects are defined, risks are ranked for frequency (or likelihood, where insufficient data exists), severity, and

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54 The researcher acknowledges that there are as many ways to perform and structure FMEA as there are sources that discuss it. For example, IEC 60812 does not explore causal factors in its version of FMEA while Dyadem explores the frequency at which the cause, rather than effect or harm, occurs. (261) (262) For a number of reasons not pertinent to risk maturity, the researcher prefers the approach defined by Dyadem and has chosen that form of FMEA for discussion in this section.
detectability, given existing controls (if any). Failure modes are ranked for their detectability, failure causes for their frequency, and failure effects for their severity, as illustrated in Figure 8-H.

Figure 8-H: Risk ranking in FMEA

The individual frequency, detectability, and severity ratings are then multiplied together to determine the RPN, which is used to prioritize risk control or as basis for risk acceptance decisions, as discussed further in section 8.4.

When performing a living risk assessment for a process, the failure modes will define the manner in which the process will fail; for example, a process parameter of mixing speed may stray outside its proven acceptable operating range, resulting in two failure modes: mix speed less than X and mix speed greater than Y. Each of these failure modes will be traced to determine failure effects, such as lack of homogeneity, and failure causes, such as mixer failure. This approach is called a
process FMEA, since the central perspective (failure mode) is related to the manufacturing process. In the event the failure of given process parameter could impact a CQA, it is, by definition, a CPP. Conversely, where a process parameter failure has no impact on a CQA, that process parameter is not critical. Using the same logic, the system-level cause of a CPP failure is a CA, while system-level cases that affect non-critical process parameters are not CAs. Figure 8-I illustrates how a process FMEA captures this segment of the failure chain.

![Figure 8-I: SmartRA process risk assessment using FMEA](image)

When used in this manner, the process FMEA will explore the severity of a CQA failure, the detectability of a CPP failure, and the frequency of a CA failure. The controls in place, or established through risk reduction, become part of the process control strategy, aimed to ensure that the failure chain never manifests through a combination of preventive measures for CA failure and control and monitoring of CPP performance, risk control strategies to be discussed further in section 8.4.

The astute reader will have noticed that the process FMEA neglects one of the components of the failure chain—CADE failure. This critical elements is explored through a system design FMEA.
The concept is the same as for the process FMEA, except that failure modes are set at the system, or CA, level. This enables the exploration of the severity of CPP failure, the detectability of a CA failure, and the frequency of CADE failure, using the risk ranking relationships described in Figure 8-H and as illustrated in Figure 8-J. Only those components that, in the event they fail, will result in CA failure are considered CADEs; components that do not affect CAs are considered non-critical.

![Failure Cause - CADE Failure](image)
![Failure Mode - CA Failure](image)
![Failure Effect - CPP Failure](image)

Figure 8-J: SmartRA system design risk assessment using FMEA

Examples of completed process and system design FMEAs for saline solution preparation using these concepts are provided in Table 8-4 and Table 8-5. The CQA of interest for this solution is concentration, which has a specification of 4.0 – 6.5 mg/mL. The risk ranking and risk evaluation criteria are shown in Table 8-6 through Table 8-9.55

55 The researcher acknowledges the limitations of ordinal risk ranking scales, as well as the use of excessively subjective ranking criteria—these limitations are explored in depth in the researcher’s published article “Risk Analysis and Ordinal Risk Ranking Scales: A Closer Look” and are briefly discussed in section 8.4.4 of this thesis. (69) Because this section is dedicated to a discussion of the living risk assessment approach, rather than the specifics of rating scales and risk calculations, the researcher has chosen to use qualitative ranking scales and risk evaluation criteria.
Table 8-4: Example process FMEA using the SmartRA approach

<table>
<thead>
<tr>
<th>Risk #</th>
<th>Failure Mode</th>
<th>Detectability Controls</th>
<th>D</th>
<th>Failure Cause</th>
<th>Preventive Controls</th>
<th>F</th>
<th>Failure Effect</th>
<th>S</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mix time &lt; 30 minutes</td>
<td>Start and end time for mixing documented in batch record</td>
<td>2</td>
<td>Timer failure</td>
<td>None</td>
<td>2</td>
<td>Concentration &lt; 4.0mg/mL</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mixer failure</td>
<td>None</td>
<td>3</td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Automation recipe is incorrect</td>
<td>None</td>
<td>5</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Timer failure</td>
<td>None</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>Mixer failure</td>
<td>None</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Automation recipe is incorrect</td>
<td>None</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Mix time &gt; 40 minutes</td>
<td>Start and end time for mixing documented in batch record</td>
<td>2</td>
<td>Timer failure</td>
<td>None</td>
<td>2</td>
<td>Delay in downstream production</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>Mixer failure</td>
<td>None</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Automation recipe is incorrect</td>
<td>None</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Mix speed &lt; 40 rpm</td>
<td>None</td>
<td>5</td>
<td>Mixer failure</td>
<td>None</td>
<td>3</td>
<td>Concentration &lt; 4.0mg/mL</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>9</td>
<td>Automation recipe is incorrect</td>
<td>None</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Beijing recipe is incorrect</td>
<td>None</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>Equipment damage</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>Mix speed &gt; 100 rpm</td>
<td>None</td>
<td>5</td>
<td>Operator error</td>
<td>None</td>
<td>3</td>
<td>Concentration &lt; 4.0mg/mL</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>11</td>
<td>Water added &gt; 1.2L</td>
<td>Water is weighed on floor scale with display</td>
<td>2</td>
<td>Floor scale failure</td>
<td>None</td>
<td>2</td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Water added &lt; 0.8L</td>
<td>Water is weighed on floor scale with display</td>
<td>2</td>
<td>Operator error</td>
<td>None</td>
<td>3</td>
<td>Concentration &gt; 6.5mg/mL</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>Floor scale failure</td>
<td>None</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Operator error</td>
<td>None</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>NaCl added &lt; 4.8g</td>
<td>NaCl is weighed on bench scale with printout</td>
<td>3</td>
<td>Operator error</td>
<td>None</td>
<td>3</td>
<td>Concentration &lt; 4.0mg/mL</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>Bench scale failure</td>
<td>None</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Water added &gt; 1.2L</td>
<td>Water is weighed on floor scale with display</td>
<td>2</td>
<td>Floor scale failure</td>
<td>None</td>
<td>2</td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Water added &lt; 0.8L</td>
<td>Water is weighed on floor scale with display</td>
<td>2</td>
<td>Operator error</td>
<td>None</td>
<td>3</td>
<td>Concentration &gt; 6.5mg/mL</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>19</td>
<td>Floor scale failure</td>
<td>None</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Operator error</td>
<td>None</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Bench scale failure</td>
<td>None</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Water added &gt; 1.2L</td>
<td>Water is weighed on floor scale with display</td>
<td>2</td>
<td>Floor scale failure</td>
<td>None</td>
<td>2</td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Water added &lt; 0.8L</td>
<td>Water is weighed on floor scale with display</td>
<td>2</td>
<td>Operator error</td>
<td>None</td>
<td>3</td>
<td>Concentration &gt; 6.5mg/mL</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>24</td>
<td>Floor scale failure</td>
<td>None</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Operator error</td>
<td>None</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Bench scale failure</td>
<td>None</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

234
<table>
<thead>
<tr>
<th>Risk #</th>
<th>Failure Mode</th>
<th>Detectability Controls</th>
<th>D</th>
<th>Failure Cause</th>
<th>Preventive Controls</th>
<th>F</th>
<th>Failure Effect</th>
<th>S</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Timer failure</td>
<td>None</td>
<td>2</td>
<td>Power outage</td>
<td>None</td>
<td>2</td>
<td>Mix time &lt; 30 min</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Timer failure</td>
<td>None</td>
<td>2</td>
<td>Insufficient/inappropriate electrical connection</td>
<td>None</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Mixer failure</td>
<td>None</td>
<td>2</td>
<td>Power outage</td>
<td>None</td>
<td>2</td>
<td>Mix time &lt; 30 min</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Mixer failure</td>
<td>None</td>
<td>2</td>
<td>Impeller damaged</td>
<td>None</td>
<td>4</td>
<td>Mix speed &lt; 40 rpm</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Mixer failure</td>
<td>None</td>
<td>2</td>
<td>Impeller incorrectly oriented (not centered properly)</td>
<td>None</td>
<td>3</td>
<td></td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>Automation recipe incorrect</td>
<td>None</td>
<td>5</td>
<td>Improper coding</td>
<td>None</td>
<td>5</td>
<td>Mix time &lt; 30 min</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>7</td>
<td>Automation recipe incorrect</td>
<td>None</td>
<td>5</td>
<td>Improper coding</td>
<td>None</td>
<td>5</td>
<td>Mix speed &lt; 40 rpm</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>8</td>
<td>Automation recipe incorrect</td>
<td>None</td>
<td>5</td>
<td>Improper coding</td>
<td>None</td>
<td>5</td>
<td>Mix speed &lt; 40 rpm</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>9</td>
<td>Automation recipe incorrect</td>
<td>None</td>
<td>5</td>
<td>Improper coding</td>
<td>None</td>
<td>5</td>
<td>Mix speed &lt; 40 rpm</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>10</td>
<td>Automation recipe incorrect</td>
<td>None</td>
<td>5</td>
<td>Improper coding</td>
<td>None</td>
<td>5</td>
<td>Mix speed &lt; 40 rpm</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>11</td>
<td>Floor scale failure</td>
<td>None</td>
<td>5</td>
<td>Power outage</td>
<td>None</td>
<td>2</td>
<td>Water added &gt; 1.2L</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>Floor scale failure</td>
<td>None</td>
<td>5</td>
<td>Sensor failure</td>
<td>None</td>
<td>3</td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>Floor scale failure</td>
<td>None</td>
<td>5</td>
<td>Weigh pan not level</td>
<td>None</td>
<td>2</td>
<td>Water added &lt; 0.8L</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>14</td>
<td>Floor scale failure</td>
<td>None</td>
<td>5</td>
<td>Weigh pan not level</td>
<td>None</td>
<td>2</td>
<td>Water added &lt; 0.8L</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>15</td>
<td>Floor scale failure</td>
<td>None</td>
<td>5</td>
<td>Weigh pan not level</td>
<td>None</td>
<td>2</td>
<td>Water added &lt; 0.8L</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>16</td>
<td>Floor scale failure</td>
<td>None</td>
<td>5</td>
<td>Weigh pan not level</td>
<td>None</td>
<td>2</td>
<td>Water added &lt; 0.8L</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>17</td>
<td>Bench scale failure</td>
<td>None</td>
<td>5</td>
<td>Power outage</td>
<td>None</td>
<td>2</td>
<td>NaCl added &lt; 4.8g</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>18</td>
<td>Bench scale failure</td>
<td>None</td>
<td>5</td>
<td>Sensor failure</td>
<td>None</td>
<td>3</td>
<td>NaCl added &lt; 4.8g</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>19</td>
<td>Bench scale failure</td>
<td>None</td>
<td>5</td>
<td>Sensor failure</td>
<td>None</td>
<td>3</td>
<td>NaCl added &lt; 4.8g</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>20</td>
<td>Bench scale failure</td>
<td>None</td>
<td>5</td>
<td>Sensor failure</td>
<td>None</td>
<td>3</td>
<td>NaCl added &lt; 4.8g</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>21</td>
<td>Bench scale failure</td>
<td>None</td>
<td>5</td>
<td>Sensor failure</td>
<td>None</td>
<td>3</td>
<td>NaCl added &lt; 4.8g</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>22</td>
<td>Bench scale failure</td>
<td>None</td>
<td>5</td>
<td>Sensor failure</td>
<td>None</td>
<td>3</td>
<td>NaCl added &lt; 4.8g</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>Rating (value)</td>
<td>Description</td>
<td>Criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Process FMEA</strong></td>
<td><strong>System Design FMEA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Insignificant / Minor Impact</td>
<td>Minor disruption</td>
<td>No impact on the performance of the product/system. The usability of the product/system is not affected.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No loss of product</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No impact on product quality or patient safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Moderately Significant / Medium Impact</td>
<td>Minor disruption</td>
<td>The performance of the product/system is reduced. The usability of the product/system is slightly affected.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deviation with no loss of product</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No impact on product quality or patient safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Significant / High Impact</td>
<td>Minor disruption</td>
<td>The performance of the product/system is greatly reduced. The usability of the product/system is greatly affected.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Portion of batch/lot must be scrapped</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minor impact on product quality. No impact on patient safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Extremely Significant / Very High Impact</td>
<td>Major disruption</td>
<td>The performance of the product/system is reduced to the point of diminished efficacy/ability to meet intended use or product/system life expectancy. The usability of the product/system is significantly impaired.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of 100% of batch/lot.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate impact on product quality. No impact on patient safety.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Catastrophic / Critical Impact</td>
<td>Failure of a critical quality attribute (CQA). Hazardous situation that may endanger patient or result in loss of data integrity.</td>
<td>Failure of a critical process parameter (CPP). Immediate or sudden loss of product/system function resulting in serious injury or death. The product/system cannot be used without successful completion of mitigation activities. Loss of data integrity.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8-7: Example frequency ranking criteria for SmartRA

<table>
<thead>
<tr>
<th>Rating (value)</th>
<th>Description</th>
<th>Qualitative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Remote</td>
<td>Failure unlikely</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>Relatively few failures</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Occasional failures</td>
</tr>
<tr>
<td>4</td>
<td>High</td>
<td>Repeated failures</td>
</tr>
<tr>
<td>5</td>
<td>Extreme</td>
<td>Failure almost inevitable or unknown</td>
</tr>
</tbody>
</table>

Table 8-8: Example detectability ranking criteria for SmartRA

<table>
<thead>
<tr>
<th>Rating (value)</th>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Very high</td>
<td>Will be detected in (nearly) every instance before it causes harm.</td>
</tr>
<tr>
<td>2</td>
<td>High</td>
<td>High likelihood of detection before it causes harm.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Moderate likelihood of detection before it causes harm.</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>Remote likelihood of detection before it causes harm.</td>
</tr>
<tr>
<td>5</td>
<td>Remote</td>
<td>Cannot / will not be detected until after the product has been used, or detectability is unknown.</td>
</tr>
</tbody>
</table>

Table 8-9: Example risk evaluation criteria for SmartRA

<table>
<thead>
<tr>
<th>RPN</th>
<th>Risk Level</th>
<th>Risk Acceptability / Required Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20</td>
<td>Low</td>
<td>Risk is acceptable. No further action required.</td>
</tr>
<tr>
<td>21 - 40</td>
<td>Medium</td>
<td>The risk must be evaluated and dispositioned as acceptable or not acceptable with appropriate rationale. Risks deemed not acceptable must be subject to risk reduction or mitigation.</td>
</tr>
<tr>
<td>≥ 41, and/or frequency or detectability = 5</td>
<td>High</td>
<td>Risk is not acceptable. Mitigation required. If continued use of the system or process will occur, interim controls must be identified to protect the patient while risk reduction is pursued.</td>
</tr>
</tbody>
</table>
8.3.3 Extracting knowledge from the living risk assessment

The SmartRA approach to risk assessment ensures a clear line of sight to the patient, regardless of the level of detail and associated distance from the patient that may result from performing risk assessments on processes and systems. The model also maximizes the amount of knowledge that can be gained, without the need to perform individual risk assessments, ensuring a holistic control strategy can be developed based on the learnings from the effort. This sub-section illustrates the knowledge that may be gained through review and interpretation of the SmartRA approach.

Identification of CPPs, CAs, and CADEs using SmartRA

As discussed above in the context of failure chains, the relationship between process parameters, manufacturing and support systems, system components and quality attributes can reveal the criticality of each and pinpoint those failures that render the patient vulnerable. ICH Q8(R2) defines CPPs as “a process parameter whose variability has an impact on a critical quality attribute;” therefore, any process parameter that, when operating outside of ranges established with a consideration to acceptable variability, could result in a CQA failure is, by definition, a CPP. (49) The relationship between process parameters and CQAs are explored through the example process FMEA developed using the SmartRA approach (Table 8-4). The process parameters that are identified as CPPs in the example include:

- Mix time (> 30 minutes)
- Mix speed (> 40 rpm)
- Water addition (0.8 – 1.2 L)
- Sodium chloride addition (4.8 – 5.2 g)
These parameters are those that, when operating outside of the specified range, could impact the CQA (concentration 4.0 – 6.5 mg/mL)—providing a direct link to the patient. On the other hand, the process parameters of “mix time > 40 minutes)” and “mix speed >100rpm” are not considered CPPs, as they do not impact CQAs.

Using the CPPs, one can then identify CAs, as follows:

- Timer
- Mixer
- Automation recipe
- Floor scale
- Bench scale

These CAs are those systems that, should they operate outside of acceptable limits, would result in CPP failure, and are “…necessary for the manufacturing process and systems to ensure consistent product quality and patient safety.” (50)

Using the SmartRA approach, the CPPs and CAs carry from the process FMEA to the system design FMEA shown in Table 8-5, which allows for the identification of CADEs, including:

- Power supply
- Electrical connections
- Integrity of the impeller
- Positioning of the impeller
- Coding of the automation recipe
- Floor scale sensor
- Bench scale sensor
- Weigh pan positioning (both floor and bench scales)

Because only critical aspects (rather than non-critical systems and functions) are explored in the system design FMEA, all component-level failure causes are deemed critical aspect design elements.

Using the SmartRA approach, the critical elements of the manufacturing process and associated systems can be identified. It is important to note that the risk ranking is not considered in the identification of these critical elements—only the causal relationships, as captured by the failure chain or failure mode/failure cause/failure effect relationships, are relevant to meet this objective.

**Informing the control strategy with SmartRA**

ICH Q8(R2) defines the control strategy as the set of controls necessary to ensure product quality and patient safety; reframed in the context of QRM, these controls are synonymous with risk controls—those controls that prevent or detect failure before the patient is impacted. (49) (45) Therefore, the control strategy can be developed directly from the learnings of the SmartRA approach, mapping to the identified CPPs, CAs, and CADEs.

One can use the SmartRA approach in a process FMEA to define CPP monitoring based on the detection score, as is the case in FMEA because failure modes are linked to detectability. The prevention of CA failure, through a review of the frequency score of the failure causes, can also be gleaned. In cases where the detectability and frequency scores are low, the prevention and
detection controls listed are adequate to include in the control strategy. However, in cases where
the detectability of a CPP or frequency of a CA failure are high, the existing controls are inadequate
and risk reduction, in the form of additional or more reliable monitoring and prevention is
necessary. Once the mitigation activities have been defined, these additional controls will be
added to the control strategy for the associated CPPs and CAs, thereby enhancing the management
of risk to the patient.

For example, using the process FMEA from Table 8-4, all identified CPPs and CAs should be
actively controlled. The control strategy should include the following in the monitoring plan for
CPPs:

- Documentation and verification of start and end mixing times
- Documentation verification of water and sodium chloride additions

In addition, a monitoring plan for the mix speed should be established, because of the lack of
existing detection controls and the associated high detectability ranking. To optimize the process
further, more reliable detection controls (such as automated recording of mix time, mix speed, and
material additions combined with alarms or equipment-stops in the event the limits are exceeded)
may be established to further reduce the risk.

Assurance that the CPPs remain within acceptable limits are provided through the CAs of the
related manufacturing systems, and the associated preventive controls. In the example process
FMEA, this includes the use of timers, mixers, automation, and weighing devices to ensure the
CPPs are met, as well as controls to ensure those systems remain in control. Based on the
preventive controls listed (none, in the example) and the related frequency rankings, controls preventing mixer failure, assuring the accuracy of the automation recipe, and preventing scale failure should be explored. The means to accomplish this are discussed in the context of validation, maintenance, and calibration strategy development later in this sub-section.

A similar analysis of the system design FMEA example in Table 8-5 reveals additional information to be included in the control strategy. CA failures, which were evaluated for frequency in the process FMEA, are now evaluated for detectability, enabling the monitoring plan to be extended to the system level. Additional preventive controls can be established using the frequency of CADE failure, and the existing risk controls. Additional benefits materialize as the QRM process continues— the adequacy of the control strategy is assessed when the residual risk is calculated and evaluated, and the ongoing effectiveness of the control strategy is explored during risk review (both concepts that are explored later in this chapter). In this way, the control strategy—inclusive of preventive and detective controls, associated limits, and ongoing effectiveness—can be derived directly from the SmartRA approach within the larger QRM framework.

Developing a validation strategy using SmartRA

FDA’s 2011 Process Validation guidance defines process validation as “the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.” (149) The process validation provides assurance of process capability, repeatability, and performance, which requires proof of the same for the manufacturing systems and instrumentation
that run the process through an equipment qualification.\textsuperscript{56} The equipment qualification consists of four sub-types: design qualification (or DQ) which ensures the system design meets the specifications, installation qualification (or IQ) which ensures that the system has been installed properly, operational qualification (or OQ) which ensures that the system operates as intended, and performance qualification (or PQ) which ensures the system can operate reproducibly within the specific parameters necessary for product manufacturing. (150) It follows that the validation strategy should focus on those critical elements identified through the SmartRA—the CPPs, CAs, and related preventive and detection controls that ensure these critical elements are functioning properly.

Using the process FMEA example shown in Table 8-4, the following pieces of equipment should be qualified:

- Timer
- Mixer
- Automated recipe
- Floor scale
- Bench scale

\textsuperscript{56} The 2011 Process Validation guidance from the FDA includes equipment qualification as a step in the overarching process validation—a step known as Phase 2a. (148) In the EU, validation and qualification remain separate concepts, as described in Annex 15. (263) With regard to the assurance of product quality and patient safety, this distinction is without a difference. The researcher has chosen to employ the terms “process validation” and “equipment qualification” (rather than “Phase 2a”) in this thesis, as these terms are more commonly used throughout the pharmaceutical and biopharmaceutical industries than those used in the US FDA guidance.
These equipment, of course, are the same systems that were previously identified as CAs. Using additional information from the system design FMEA example in Table 8-5, a more complete qualification strategy can be developed, as shown in Table 8-10.

**Table 8-10: Example qualification strategy derived from SmartRA approach**

<table>
<thead>
<tr>
<th>System</th>
<th>Element to test</th>
<th>Qualification type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timer</td>
<td>Electrical connections</td>
<td>IQ/OQ</td>
</tr>
<tr>
<td>Mixer</td>
<td>Impeller damage</td>
<td>IQ/OQ</td>
</tr>
<tr>
<td>Mixer</td>
<td>Impeller positioning</td>
<td>IQ/PQ</td>
</tr>
<tr>
<td>Automation recipe</td>
<td>Coding</td>
<td>IQ/PQ</td>
</tr>
<tr>
<td>Automation recipe</td>
<td>Security measures to prevent authorized changes to code</td>
<td>IQ/PQ</td>
</tr>
<tr>
<td>Floor and bench scales</td>
<td>Sensor</td>
<td>IQ</td>
</tr>
<tr>
<td>Floor and bench scales</td>
<td>Weigh pan positioning</td>
<td>IQ</td>
</tr>
<tr>
<td>Floor and bench scales</td>
<td>Print function for bench scale</td>
<td>IQ/OQ/PQ</td>
</tr>
</tbody>
</table>

Validation of the process would focus on ensuring that the manufacturing systems adequately support the process, and that the process yields product of the appropriate quality. In this way, qualification and validation *reduce uncertainty* associated with the process and manufacturing system performance by providing data that precisely reflects upon the risks identified through the SmartRA approach. Following qualification and validation, the risk ranking may need to be adjusted to better reflect the additional knowledge gained. Requalification and revalidation, performed at defined intervals or based on planned changes and reviews, provides further assurance over the course of the product lifecycle and can be coupled with risk review to maximize the use of data trends and analysis.

**Developing a maintenance and calibration strategy using SmartRA**

Finally, the knowledge gained from the SmartRA approach can be used to develop (and subsequently adjust) maintenance and calibration activities for CAs and CADEs. This is easily
demonstrated using the system design FMEA example from Table 8-5. The identified CADEs each have an associated frequency of failure, since the CADEs serve as failure causes within a system design FMEA. Maintenance (ideally preventive, rather than corrective, in nature) should be performed on all CAs and CADEs. During maintenance, the system should first be inspected for overt damage and wear and tear, allowing for a window of opportunity to detect failure of the system as whole. Specific inspections, based on the CADEs identified and their vulnerability to failure, may also be included. The inspection is followed by maintenance activities, which are defined based on the system design FMEA. Table 8-11 suggests a list of maintenance activities that should occur for each system (CA) listed.

Table 8-11: Example maintenance strategy using SmartRA

<table>
<thead>
<tr>
<th>System</th>
<th>Component</th>
<th>Maintenance activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timer</td>
<td>Electric wiring</td>
<td>Inspect wiring for damage. Replace as needed (not to exceed 10 years, based on metallurgical properties of the wiring). Follow with calibration.</td>
</tr>
<tr>
<td>Mixer</td>
<td>Impeller</td>
<td>Inspect impeller for damage. Ensure all surfaces are smooth with no gashes, warping, or metal damage (such as rust). Replace when impeller integrity is compromised (not to exceed 15 years based on material of construction lifespan). Test impeller to ensure it is properly positioned within vessel. The shaft of the impeller should be positioned perpendicular with respect to the vessel floor and parallel with the vessel walls. Follow with calibration.</td>
</tr>
<tr>
<td>Automation recipe</td>
<td>Coding</td>
<td>Review audit trail associated with the code to ensure it has not changed. Take appropriate action based on findings.</td>
</tr>
<tr>
<td>Floor and bench scales</td>
<td>Weigh pan positioning</td>
<td>Clean under the weigh pan to remove any particulate that may alter the positioning of the weigh pan on the sensors. Inspect weigh pan to ensure the metal is not warped and the surface remains level. Follow with calibration.</td>
</tr>
</tbody>
</table>
The frequency at which system maintenance and instrument calibration should occur can also be derived from the SmartRA approach. While the initial maintenance and calibration intervals for new systems or instruments may be established based on supplier recommendations combined with the firm’s historical of similar systems, any increases in failure rates (manifesting as increases in frequency ranking) identified during risk review should trigger a review and potential increase of the frequency at which maintenance and calibration is performed, or the system replaced.

The SmartRA approach offered as an example of maturity of risk assessment may appear to be quite an obvious model for pharmaceutical and biopharmaceutical companies. Indeed, it is. Despite its elegant simplicity, the researcher has not identified companies making use of this or similar approaches during the Phase 2 or 3 research. Quite the contrary—philosophical dialogues and literature reviews revealed that many firms spend time and energy performing process and system design FMEA and fail to evaluate critical elements at all. The researcher infers that risk assessments of non-critical things likewise fail to add value, either to the organization or the patient. The SmartRA approach offers a direct connection to the patient by using critical elements as the foundation for risk assessment (and therefore subsequent risk control, risk review, and risk communication). It also provides an operational benefit—streamlining the QRM process and minimizing “noise” that may result from excessive numbers of risk assessments can ensure that QRM is simplified, but not simplistic. It allows the organization to focus on managing risk to the patient, rather than “doing QRM.” It is therefore set as the benchmark of maturity with regard to risk assessment.
8.4 Maturity with regard to risk control

As discussed in Chapter Six with respect to ISO 14971, risk control is perhaps the most important aspect of the risk management lifecycle. It is when companies must act to improve (or maintain) product quality and reduce risk to the patient, and is therefore deserving of a proportionate level of analysis, resource commitment, and intellectual energy within a QRM program. Yet many companies do not treat risk control with the appropriate attention, choosing instead to implement questionably effective controls such as procedural revisions and re-training of operators or analysts instead of striving for more effective and permanent solutions. (128) Maturity with regard to risk control would assure careful consideration, vetting, and implementation of measures to reduce risk.

8.4.1 Fundamentals of risk control

Vesper distinguishes between two fundamental types of risk control (also described as “mitigation”): preventive and protective. Preventive mitigation aims to prevent the risk from occurring. These types of mitigation activities are typically designed to eliminate the risk completely or to reduce the likelihood of a given risk. Protective mitigation seeks to protect the product or patient in the event the risk occurs, through either increasing the detectability of a failure that has already occurred, or breaking the causal chain between hazard and harm. (61) Preventive mitigation is typically preferred over protective mitigation, as it targets underlying quality issues within the process or system being assessed and can increase reliability accordingly.

For example, in the FMEA shown in Table 8-12, a preventive mitigation might be one that reduces the frequency score (e.g., increasing the frequency of gasket replacement or changing the gasket
material to one that generates fewer particles). A protective mitigation would reduce the
detectability score (e.g., improve visual inspection for particulates) or break the causal chain
between the failure mode and failure effect (e.g., implementing a downstream filtration step that
would remove particles from the product prior to patient exposure). In this example, the preventive
mitigations are a better choice than the protective, although a combination may be used to better
manage the risk to patient.

Table 8-12: Example FMEA to illustrate preventive and protective mitigation activities

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>Detectability</th>
<th>Failure Cause</th>
<th>Frequency</th>
<th>Failure Effect</th>
<th>Severity</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particulates present in product</td>
<td>3</td>
<td>Degradation of gasket</td>
<td>4</td>
<td>Adverse event in patient</td>
<td>5</td>
<td>60</td>
</tr>
</tbody>
</table>

As discussed in Chapter Six, ISO 14971 describes several general risk mitigation techniques,
listing them in priority order according to effectiveness. This list, as interpreted by the researcher
for the pharmaceutical and biopharmaceutical industries, includes:

- Design/process changes - This type of mitigation involves the alteration of the product,
equipment, or process design to redefine the overall risk profile (e.g., through the
addition of fail safes, process simplification, automation). Design changes are typically
the most effective type of mitigation that can reduce or eliminate risk; however,
substantial cost and resources are often involved and the design changes may introduce
new risks to the overall process.

- Safeguarding - This type of mitigation focuses on shielding the hazard to contain its
impact, installing redundant backups, implementing in-process or release testing to
confirm quality prior to further processing, or implementing alarms/warning that allow
for immediate intervention. Safeguarding tends to be less effective than design changes at
reducing risk, although when used judiciously to impact specific risks can successfully reduce risk to the patient.

- Descriptive safety means - This type of mitigation focuses on providing written and verbal instruction regarding the presence of certain risks and offers methods to avoid or otherwise control them when they occur. Examples include instruction within an SOP, production record, or literature accompanying the product, and the associated training. Due to the reliance on human intervention, this mitigation technique tends to be less robust than design changes or safeguarding, however, due to the relative ease of implementation, this technique is often the most widely used in pharmaceutical and biopharmaceutical industries.

The risk control options available to reduce a given risk will, of course, vary, depending on the nature of the risk.

### 8.4.2 Selecting risk controls

One approach to the selection of risk controls entails an evaluation of each option as to the impact it would have on risk reduction. The tool below can be used to illustrate the strengths and limitations of each risk control option to better communicate the rationale for selection of a given risk control strategy. The scoring model has been developed to apply a weighting to the effect of each risk control option, in that more effective results (such as elimination of one or more risks) carries more weight than do less effective results (such as improving the detectability of one or more risks). The scoring method is optional; while scoring adds a layer of complexity to the risk control option analysis, it allows for a more objective relative ranking of each option which may be desired in certain circumstances. It is important to note that the mathematical result from the scoring model shown below has no meaning in itself; it exists merely to demonstrate the relative benefit of each risk control option in the context of QRM. In the event a qualitative (rather than
A simple check box approach may be used. In example provided in Table 8-13, risk control option #2 provides the greatest benefit in terms of risk reduction and would be the best option of those listed.

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Scoring</th>
<th>Risk Control Option #1</th>
<th>Risk Control Option #2</th>
<th>Risk Control Option #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminates the risk</td>
<td>+ (4 x [number of risks eliminated])</td>
<td>+ (4 x 3) = + 12</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Alters the harm (reduces severity)</td>
<td>+ (3 x [number of risks with reduced severity])</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Prevents, but does not eliminate, the risk from occurring</td>
<td>+ (2 x [number of risks with reduced likelihood])</td>
<td>N/A</td>
<td>+ (2 x 8) = + 16</td>
<td>N/A</td>
</tr>
<tr>
<td>Increases the detectability of the risk before it causes harm</td>
<td>+(1 x [number of risks with improved detectability])</td>
<td>N/A</td>
<td>N/A</td>
<td>+ (1 x 10) = + 10</td>
</tr>
<tr>
<td>Introduces new risk(s)</td>
<td>- [4 x [number of new risks introduced]]</td>
<td>- (4 x 2) = - 8</td>
<td>N/A</td>
<td>- (4 x 1) = - 4</td>
</tr>
<tr>
<td>Increases severity of one or more risks</td>
<td>- (3 x [number of risks with increased severity])</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Increases likelihood of one or more risks</td>
<td>- (2 x [number of risks with increased severity])</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Reduces detectability of one or more risks</td>
<td>- (1 x [number of risks with increased severity])</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>16</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

While the risk control option analysis model enables QRM practitioners to critically evaluate mitigation activities and select amongst them, there is core vulnerability associated with the method—that a single risk control option should be selected. The review of defense in depth principles in Chapter Six revealed that layered controls, or combinations of controls, often offer more complete and reliable risk control than does a single option. Where resources and technical
feasibility permit, combinations of risk controls should be explored in order to more fully manage risk to the patient.

8.4.3 Additional points to consider in the development of a risk control strategy

Anticipated effectiveness of each mitigation activity (or combination of mitigations) is only one consideration in the selection of risk controls. Improvements in risk maturity require the mitigation of individual risks to be considered as component parts of an overarching risk control strategy, comprised of:

- “GMP” controls, such as those required to achieve compliance with international and local law (90)
- Existing controls that were taken into consideration during the risk assessments, such as those incorporated in the quality system and existing process and equipment design
- Newly identified mitigation activities as determined through the risk assessment

In a mature QRM program, optimized risk control strategies will be developed in consideration of several points, including which activities should be prioritized for implementation, what aspect of the risk should be targeted for control, the anticipated completeness of risk control, the anticipation of any new or changed risks that might be introduced through implementation of the risk controls, the need for interim controls, and the availability of resources.

Prioritizing risk control

For risks identified through a qualitative risk-ranking scale (e.g., high, medium, low; as in Hazard Analysis and Critical Control Points and Risk-Based Impact Assessment), mitigation of high risks
should take priority over mitigation of medium risks, which are further prioritized over mitigation of low risks. For example, in the HACCP shown in Table 8-14, mitigation of Risk #2 should take priority over Risk #1.

Table 8-14: Example HACCP to illustrate the prioritization of risk control

<table>
<thead>
<tr>
<th>Risk #</th>
<th>Hazard</th>
<th>Likelihood</th>
<th>Severity</th>
<th>Risk Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Introduction of microbial contamination</td>
<td>Remote</td>
<td>Critical</td>
<td>Medium</td>
</tr>
<tr>
<td>2</td>
<td>Introduction of particulate contamination</td>
<td>Average</td>
<td>Critical</td>
<td>High</td>
</tr>
</tbody>
</table>

For risks identified through a semi-quantitative ranking scale (e.g., Risk Priority Number or RPN; as in Failure Modes and Effects Analysis) mitigation priority is from the highest RPN to the lowest RPN. For example, the FMEA shown in Table 8-15, the priority for mitigation, from highest to lowest, is Risk #1, Risk #2, then Risk #3.

Table 8-15: Example FMEA to illustrate the prioritization of risk control

<table>
<thead>
<tr>
<th>Risk #</th>
<th>Failure Mode</th>
<th>Detectability</th>
<th>Failure Cause</th>
<th>Frequency</th>
<th>Failure Effect</th>
<th>Severity</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Introduction of microbial contamination</td>
<td>2</td>
<td>HEPA failure</td>
<td>4</td>
<td>Loss of 100% of batch</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>Poor aseptic technique</td>
<td>3</td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>Breach of closed system</td>
<td>2</td>
<td></td>
<td></td>
<td>16</td>
</tr>
</tbody>
</table>
Determining the target of risk control

Where there are opportunities to implement design changes to the system or process that was evaluated through the risk assessment, risk control should seek to eliminate the hazard/risk altogether. In the FMEA shown in Table 8-16, for example, the mitigation effort should focus on eliminating the use of animal-derived raw materials, thereby eliminating the source of the risk.

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>Detectability</th>
<th>Failure Cause</th>
<th>Frequency</th>
<th>Failure Effect</th>
<th>Severity</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmissible Spongiform Encephalopathy (TSE) present in finished product</td>
<td>5</td>
<td>Use of animal-derived raw material (serum)</td>
<td>5</td>
<td>Severe adverse event or death (unsafe product)</td>
<td>5</td>
<td>125</td>
</tr>
</tbody>
</table>

In the event the risk cannot be completely eliminated, risk controls should be tailored to directly impact the element of risk that is driving the unacceptable ranking (e.g., frequency or detectability). For example, risk controls for the example FMEA in Table 8-17 should focus on increasing the detectability of the failure mode (reducing the detectability ranking; making the pH level more detectable), while risk control for the HACCP in Table 8-18 should focus on reducing the likelihood that the hazard will occur (preventing metal particulates from being introduced into the solution).
Table 8-17: Example FMEA to illustrate the target of risk control

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>Detectability</th>
<th>Failure Cause</th>
<th>Frequency</th>
<th>Failure Effect</th>
<th>Severity</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH too low</td>
<td>5</td>
<td>Too much HCl added</td>
<td>1</td>
<td>Cell death</td>
<td>4</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 8-18: Example HACCP to illustrate the target of risk control

<table>
<thead>
<tr>
<th>Hazard</th>
<th>Likelihood</th>
<th>Severity</th>
<th>Risk Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction of metallic particulates in solution to be sterile filtered</td>
<td>Frequent</td>
<td>Minor</td>
<td>High</td>
</tr>
</tbody>
</table>

Anticipating the completeness of risk control

When planning mitigation activities for a given risk, QRM practitioners should consider whether the proposed activity will be sufficient to reduce the risk to an acceptable level (i.e. whether the anticipated residual risk will fall within acceptable limits defined by the firm’s risk tolerance). If the proposed activity will be insufficient to reduce the risk to an acceptable level, alternative or additional risk control should be proposed and implemented in parallel. For example, in the FMEA shown in Table 8-19, a mitigation activity of "implement a Preventive Maintenance (PM) program or HEPA filters" may have been proposed by the team. This control is expected to reduce the frequency score to a 2 (once PM is implemented, the HEPAs will fail less often). However, the RPN will remain at an unacceptable level (in this example, 32), due to low detectability. Therefore, the anticipated residual risk is not acceptable and additional mitigation activities (such as air-borne particulate monitoring) should be explored.
Table 8-19: Example HACCP to illustrate completeness of risk control

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>Detectability</th>
<th>Failure Cause</th>
<th>Frequency</th>
<th>Failure Effect</th>
<th>Severity</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unacceptable levels of airborne particulates present</td>
<td>4</td>
<td>HEPA filter failure</td>
<td>4</td>
<td>Contamination of product with viable or non-viable particulates</td>
<td>4</td>
<td>64</td>
</tr>
</tbody>
</table>

Anticipating the introduction of new risks

As the risk control strategy is being planned, the QRM practitioner should consider whether the proposed activity will introduce any new risks into the system or process, and take to minimize these new risks. Prior to the acceptance of residual risk, these new risks must be further analyzed in the risk assessment and will be subject to risk control, based on the associated risk level. In the example FMEA in Table 8-20, a mitigation activity of "eliminate the use of serum in the cell culture process" has been proposed by the team. While this mitigation successfully eliminates the hazard of concern, there may be additional risks that arise when serum is no longer used (such as slow or no cell growth due to the absence of necessary growth factors). The additional risks should be explored and further mitigation (replacement of missing growth factors) implemented.

Table 8-20: Example FMEA to illustrate the introduction and prospective mitigation of new risks

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>Detectability</th>
<th>Failure Cause</th>
<th>Frequency</th>
<th>Failure Effect</th>
<th>Severity</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmissible Spongiform Encephalopathy (TSE) present in finished product</td>
<td>5</td>
<td>Use of animal-derived raw material (serum)</td>
<td>5</td>
<td>Severe adverse event or death (unsafe product)</td>
<td>5</td>
<td>125</td>
</tr>
</tbody>
</table>
Anticipating an impact to other risks

In addition, proposed risk controls may affect the risk level or state of control for other identified risks. Care should be taken to minimize a negative peripheral impact of a mitigation activity. The impact to any other risks must be further analyzed in the risk assessment and may necessitate the need for re-ranking of affected risks. In the HACCP shown in Table 8-21, for example, a mitigation activity of "sanitize work surface with a sporicidal solution prior to each use" may have been proposed by the team to reduce the likelihood of microbial contamination of the lab bench. However, if the particular sporicidal solution is corrosive, it might increase the likelihood of surface pitting of the lab bench. If this is the case, an alternative risk control should be explored, or if there are no other viable alternatives, the likelihood rating of rouging should be increased to reflect the actual level of risk.

Table 8-21: Example HACCP to illustrate changes to other risks introduced through risk control

<table>
<thead>
<tr>
<th>Hazard</th>
<th>Likelihood</th>
<th>Severity</th>
<th>Risk Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbial contamination of lab bench work surface</td>
<td>Frequent</td>
<td>Serious</td>
<td>High</td>
</tr>
<tr>
<td>Rouging / pitting of stainless steel lab bench work surface</td>
<td>Unlikely</td>
<td>Minor</td>
<td>Low</td>
</tr>
</tbody>
</table>

Evaluating the need for interim controls

In certain instances, the length of time necessary to implement sufficient risk control warrants the design or definition of interim controls. This is due to the continued exposure of the product, process, system, and patient to the risk until mitigation activities are in place and proven effective; the implementation and evaluation of interim controls may be necessary to contain the problem
and adequately manage the risk to the patient until full control has been achieved. For example, in the FMEA shown in Table 8-22, the team proposed design changes (machining of the filling needles to reduce the diameter) to mitigate the associated risk. These design changes are expected to span a significant period prior to full implementation. While the supporting data is being gathered, the unacceptable risk continues to be a concern, and interim controls (such as increased inspection for metal particles or glass damage prior to product release) should be employed to reduce the vulnerability until the long-term risk control can be fully vetted, validated, and deployed.

**Table 8-22: Example FMEA to illustrate the need for interim controls**

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>Detectability</th>
<th>Failure Cause</th>
<th>Frequency</th>
<th>Failure Effect</th>
<th>Severity</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filling needle may contact inner rim of vials during filling</td>
<td>4</td>
<td>Filling needle diameter too large</td>
<td>4</td>
<td>Metallic particulates present in finished product</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Glass damage to vial</td>
<td>5</td>
<td>80</td>
</tr>
</tbody>
</table>

**Resourcing**

The amount of available resources should be considered during the development of a risk control strategy; after all, a firm with infinite resources would have little need to prioritize risks and associated controls. (127) Resources often include money, time, and expertise—each of which is limited to some extent in a business environment. While the prioritization of risks for reduction, described earlier in this section, provides a mechanism to allocate resources in risk control, companies mature in QRM implementation will also consider whether the level of effort and
amount of resources to be expended are proportional to the level of risk. In the FMEA shown in Table 8-23, for example, the team proposed that the process be automated, which could eliminate the failure mode altogether. However, automating the process would require large amounts of resources that might be better spent reducing other risks more relevant to the patient. The team should explore the benefits of automation in reducing the risk, the total associated resource expenditure, and alternate risk reduction options to assist with decisions on risk mitigation.

**Table 8-23: Example FMEA to illustrate the consideration of available resources for risk control**

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>Detectability</th>
<th>Failure Cause</th>
<th>Frequency</th>
<th>Failure Effect</th>
<th>Severity</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to follow SOP</td>
<td>3</td>
<td>Operator error</td>
<td>3</td>
<td>Loss of 100% of batch</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procedure unclear</td>
<td>2</td>
<td></td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

A risk control strategy indicative of a high level of risk maturity takes into account the effectiveness of proposed controls and the completeness of control and the need for combinations of controls, as well as other factors. The application of controls is prioritized based on the level of risk, and tailored to directly impact the element of risk that is driving an unacceptable classification. Any new or changed risks that may be introduced through the implementation of risk controls are actively anticipated and prospectively mitigated. In this way, the patient is best protected.

### 8.4.4 Accepting the residual risk

Residual risk acceptance is not a topic that has merited much discussion in industry or regulatory circles. ICH Q9 offers minimal guidance on this step, simply stating:
“Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.” (45)

Curiously, of those responsibilities of decision makers listed in ICH Q9, risk acceptance is not included. Not surprisingly, the dearth of information on risk acceptance in the pharmaceutical and biopharmaceutical industries has led to some practices that indicate a lack of understanding of QRM principles and the need for patient protection. Lorianne Richter, Senior Consultant with ValSource, notes that signs of a mature QRM program include “…understanding risk reduction versus risk acceptance, documenting risks that have been accepted, and really understanding risk tolerance.” (129)

Philosophical dialogues from the Phase 2 and 3 research revealed that a typical company (having a low-to-moderate level of risk maturity as discussed in Chapter Five), accepts residual risk through a comparison between the risk level and risk acceptance tables or action levels. (128) Where the risk level exceeds a defined threshold, the risk is considered unacceptable and additional risk reduction must be pursued. Risks below that threshold are considered acceptable with no further inquiry. (130) This practice does not evaluate residual risks case-by-case, as suggested by ICH Q9, nor does it distinguish between risks with a potential impact to the patient and those that do not. In addition, this practice does not assign responsibility and accountability for risk acceptance to any individual party—policies and procedures do not accept risk; people do. It is
the opinion of this researcher that decision makers, rather than documents or lower-level personnel, should be held responsible for risk acceptance.

Industries mature in risk management offer some insight into mature practices for the evaluation and acceptance of residual risk, as reviewed in Chapter Six. The first learning that can improve risk maturity and the management of risks to the patient is including both an evaluation of individual residual risks and the overall residual risk posed by the product, process, or system. The overall residual risk should be evaluated in light of the medical benefits offered to the patient, as discussed in ISO 14971 and the external (patient) context, as discussed in ISO 31000. For example, if there are numerous identified risks that could jeopardize product quality or patient safety, the decision maker should determine whether, on balance, the patient would be better served through exposure to those risks given the benefits they would expect to receive through the medicinal product, or whether the risks outweigh those benefits.

In some cases, the scope of the risks subject to acceptance may not be of the nature that the patient is affected; for example, those that may manifest as product loss or production delays. However, in certain circumstances, such in instances of drug shortage or where product time directly relates to product efficacy (as is the case with radiological therapies), those same consequences may extend to the patient. Decision makers should therefore evaluate the external context with respect to the patient when making risk acceptance decisions.

Individual residual risks are also subject to acceptance, in a slightly different context. Mature QRM programs can employ the “acceptance threshold” approach described earlier in this section, provided the thresholds were developed in an appropriate way. Risk acceptance thresholds should
directly reflect the firm’s risk tolerance for the particular product, patient population, and external context. The acceptance thresholds should be carefully compared with the specific risk rating criteria and algorithm inherent in all risk tools to ensure that the derivation of the risk level (i.e. the specific combinations of likelihood, severity, and where used, detectability) are appropriate given the threshold. This is particularly challenging for risk tools that apply arithmetic to ordinal ranking scales, such as FMEA.\textsuperscript{57}

For example, an RPN of 20 in an FMEA that employed 1-5 rating scales for frequency, detectability, and severity can be the result of eight possible combinations, as shown in Table 8-24\textsuperscript{58}:

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Frequency</th>
<th>Detectability</th>
<th>Severity</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>D</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>E</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>F</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>G</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>H</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

\textsuperscript{57} It should be noted that FMEA, as described in IEC 60812, results in a Risk Priority Number, or RPN, and not a risk level such as high, medium, or low. The intent of the RPN is just as it sounds—to prioritize risks relative to one another. FMEA was not designed to be used with such qualitative measures of risk or risk acceptability thresholds. Despite this, many pharmaceutical and biopharmaceutical companies add on the artificial construct of acceptability, dividing RPNs into “buckets” intended to represent high, medium, and low risks. This practice tends to bias towards lower risk scores and therefore may not motivate the firm to take action where needed. Without a complete understanding of the tool design and the shortcomings of ordinal risk ranking scales, it is unlikely that these companies will reach a high level of maturity with regard to risk acceptance.\textsuperscript{58}

\textsuperscript{58} The discussion of risk acceptance through ordinal ranking scales was previously published by the researcher. (69)
While the RPN is the same in each case, the eight situations above represent quite different risk scenarios that should be considered individually with regards to acceptability. For example, scenarios A, C, and E all represent instances in which the consequences are incredibly dire (severity = 5). However, the narratives associated with these scenarios differ significantly. In scenario A, for example, we have what might be considered a “black swan” event—one that is rare yet catastrophic. The scenario is very unlikely to occur (frequency = 1), however if it did, it’s improbable we would know about it (detectability = 4) before the catastrophic outcome (severity = 5) is realized. Conversely, in scenario E, we have a risk or failure that occurs quite often (frequency = 4), but we can detect it readily (detectability = 1) before the catastrophic consequence (severity = 5) transpires. Scenario C represents a middle ground, where a failure that could pose a severe consequence (severity = 5) is fairly infrequent (frequency = 2) and readily detectable (detectability = 2). These risk scenarios are of course all different, but this is not evident when one only considers the RPNs, without taking into account the individual scores that gave rise to those RPNs. The RPNs alone do not indicate where the differences lie. Thus, when RPN thresholds are used to determine whether risk reduction or acceptance is warranted, flawed decision-making is often the result.

In order to ensure the appropriate risk acceptance decisions are made, companies mature in QRM apply a second set of considerations to be used in concert with the RPN. For example, a company may require any risk with a severity score of 5 to be reduced as low as possible, irrespective of the RPN, since such scenarios could result in a significant impact to process, product, or patient and should be handled with those consequences in mind. A company may also require risks with a frequency or detectability of 5 to be reduced as well, as in many cases these are indicative of lack of effective process controls. These considerations can be added to an analysis of the RPN to assist
with decisions regarding residual risk acceptance, to ensure the firm’s risk tolerance is adequately and consistently represented.

8.5 Maturity with regard to risk review

As mentioned briefly in Chapter Four, risk review tends to be the most neglected portion of the QRM lifecycle. Risk review is when new knowledge gained over the product lifecycle is used to reflect upon the risk, and is performed to determine whether QRM has been effective and whether updates to the risk assessment or risk control strategy are warranted in light of changing conditions.

ICH Q9 notes of risk review:

“A mechanism to review or monitor events should be implemented… Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk.” (45)

The understanding of the purpose and process of risk review throughout the pharmaceutical and biopharmaceutical industries is rather weak. The lack of literature on the topic, as well as multiple philosophical dialogues throughout the Phase 2 and 3 research, attest to this. At the PDA Annual Meeting in April 2017, one delegate from a large pharmaceutical company stated, “[my company] doesn’t see the value in risk review. We just figure that if the process hasn’t changed, there is no need to update the risk assessment.” Several other delegates confessed that their companies have not yet performed risk review, with one noting that their company “just got [cited by a regulatory
agency] on that… Most of our risk assessments were put on the shelf and never looked at again. Most of [the assessments] are over six years old.”

These anecdotes are clearly indicative of immature QRM programs—programs missing the opportunity to exploit risk review for the purposes summarized in ISO 31000:

- “…ensuring that controls are effective and efficient in both design and operation;
- obtaining further information to improve risk assessment;
- analyzing and learning lessons from events (including near-misses), changes, trends, successes and failures;
- detecting changes in the external and internal context, including changes to risk criteria and the risk itself which can require revision of risk treatments and priorities; and
- identifying emerging risks.” (15)

Mature programs acknowledge the value risk review offers both as a continuous improvement tool and for ongoing protection of the patient. One need only to refer to complacency at NASA, as discussed in Chapter Six, to understand how building new information into an existing risk assessment can help save lives. There are several considerations into risk review that are addressed in increasingly robust ways as risk maturity increases: when risk review is performed, the data and knowledge that serves as an input to the review process, and how those data impact previously-conducted risk assessments and QRM decisions.

8.5.1 Types of risk review—periodic v. event-driven

Risk review is the process where the output/results of the risk management process are reviewed to ensure the risks remain acceptable considering changing conditions and new knowledge and
experience. As mentioned in section 8.1, living risk assessments cover an entire product, process, or system over its lifecycle and are therefore subject to risk review. Ad hoc risk assessments, on the other hand, are performed to address a specific event at a given point in time and need not continue through the QRM lifecycle to risk review. The objective of risk review is to ensure that living risk assessments continue to reflect the current state of the product, process, or system with regard to identified risks, risk levels, and acceptance decisions. Risk review also provides assurance that the identified risk controls continue to effectively maintain risk within acceptable limits.

Risk review should be performed following residual risk acceptance; in the event the risk has not yet been accepted, other aspects of the QRM lifecycle are still in play and the review phase has not yet been reached. While this is evident based on the flow of the QRM lifecycle in ICH Q9, some companies begin risk review before risk reduction is complete, which may confuse the objectives of the effort. (128) As one delegate at the April 2017 PDA Annual Meeting noted, “[my company] has [historically] used risk review to follow up on open mitigation activities and close out the risk assessment.” This practice changes the intent of risk review from one of reflective learning to one redundant to an earlier QRM process step—namely, risk control.

In order to glean the greatest benefit from risk review, two types should be employed: periodic and event-driven. Periodic risk reviews occur at a defined interval, based on the level of risk associated with the topic of the QRM effort. Periodic risk reviews are comprehensive and include an evaluation of all data, information, and knowledge gained since the prior periodic risk review. Event-driven risk reviews, on the other hand, occur based on a trigger within the quality system, operating condition, or internal or external business climate. These types of reviews should
generally be more targeted and specific than periodic risk reviews, and entail an evaluation of the impact of a particular data set or event on the risk assessment.

ICH Q9 implies that the frequency of periodic risk review be based upon the level of risk identified in the risk assessment; it is the opinion of this researcher, however, that the frequency of periodic risk review should be established based on the risk inherent to the topic and the anticipated rate at which the risk assessment contents might become stale or obsolete. After all, it is unlikely that a critical or complex manufacturing process, having reached the point where all identified risks are well-controlled and acceptable, will suddenly become static both in the process details and the firm’s knowledge and understanding of that process. It is therefore fruitful to assign a discrete periodic risk review interval to each living risk assessment based on the criticality of the topic and the anticipated (or actual) rate of change and knowledge accrual. The researcher proposes that a simple risk tool be used to facilitate this decision. The tool includes the assignment of a topic criticality rating using the criteria in and a rate of change rating using the criteria in Table 8-25 and Table 8-26. The intersection of these two ratings in Figure 8-K offers an appropriate periodic risk review interval for the particular living risk assessment.

Table 8-25: Topic criticality ratings and criteria

<table>
<thead>
<tr>
<th>Rating</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Minor   | Product: Product intermediate  
          Process/System: Support processes and associated equipment/systems, such as solution/media preparation, packaging and labeling processes and equipment, component preparation, or general use utilities.  
          Facility: Uncontrolled and controlled-not-classified (CNC) cleanrooms. |
| Moderate| Product: Non-sterile products, or non-life-saving/life-sustaining product that are not at risk of shortage. |
Critical

Process/System: Upstream processing and associated equipment, such as API production, and quality control methods not associated with product release.

Facility: Grade C cleanrooms

Process/System: Downstream processing and associated equipment, such as purification and fill/finish, and quality control methods associated with product release.

Facility: Grade A and B cleanrooms.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Product, process, or system is mature (in the commercial phase of the product lifecycle); additional learnings have plateaued.</td>
</tr>
<tr>
<td></td>
<td>Actual (historical) or anticipated rate of change of the product, process, system, or facility under assessment is rare (e.g. less than two significant changes per year).</td>
</tr>
<tr>
<td>Average</td>
<td>Product, process, or system has recently entered the commercial phase of the product lifecycle; additional learnings are expected as experience is gained.</td>
</tr>
<tr>
<td></td>
<td>Actual (historical) or anticipated rate of change of the product, process, system, or facility under assessment is average (e.g. between two and four significant changes per year).</td>
</tr>
<tr>
<td>Frequent</td>
<td>Product, process, or system is in the development phase of the product lifecycle; significant and frequent knowledge gains are expected.</td>
</tr>
<tr>
<td></td>
<td>Actual (historical) or anticipated rate of change of the product, process, system, or facility under assessment is frequent (e.g. more than four significant changes per year).</td>
</tr>
<tr>
<td>Rate of Change</td>
<td>Topic Criticality</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Frequent</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>

As with all risk tools, the specific numerical criteria and examples, as well as the periodic risk review intervals themselves, should be evaluated in the context of a given firm’s product portfolio and quality system conditions and tailored as appropriate.

In addition, companies should also define circumstances, events, and data trends that should trigger an event-driven risk review, for example:

- A critical deviation occurs that represents a previously-unknown risk
- A significant change is proposed that may introduce new risks to the overall process or system
- A trend is identified that may warrant adjustment of the identified risks/risk levels in the living risk assessment
- A significant complaint is received that may affect the identified risks/risk levels in the living risk assessment
• Changes in inventory levels with the product (or similar competitor products) render the drug more or less susceptible to shortage
• The indication or patient population for the drug changes (e.g. approved for use in pediatrics)
• A request for an event-driven risk review is received from internal or external stakeholders

Such events would require a reevaluation of identified risks, risk levels, or risk tolerance and resultant risk acceptance decisions given the new information.

8.5.2 Performing a risk review

Despite the fact that information on risk review in the pharmaceutical and biopharmaceutical industries is sparse, once again industries mature in risk management have many lessons to offer. ISO 14971, for example, lists a variety of data that should be reviewed as part of the product/post-production phase of the medical device risk management lifecycle. A basic list of information inputs into periodic risk review includes:

• Related deviation/investigation data
• Related customer complaint and adverse event data
• Related change management data
• Related ad hoc risk assessments
• Documented sources of high uncertainty in the original risk assessment
• Recommendations or “parking lot” issues from the original risk team
• Related regulatory trending data, such as new or changed standards and guidance documents
• Related industry trending data and scientific publications (e.g. applicable data from scientific journals, industry magazines, technical reports, whitepapers, or conferences)
• Related data from suppliers, sister sites, contract manufacturers, service providers, and business partners
• Additional quality system data as applicable to the topic of the risk assessment (e.g. quality control, computer systems, validation and qualification, automation records)

Event-driven risk reviews are typically smaller in scope than periodic risk reviews, may only require those data related to the trigger event to be evaluated.

These data should be reviewed to determine what impact, if any, the data and resultant new knowledge has on the living risk assessment. For example, hazards might be present that were previously unknown or unrecognized—these hazards might be reactively identified where realized, or they may be proactively identified through data sources that allow for such anticipation. The risk levels, or individual risk ratings, may have changed, as might be the case when moving from a likelihood scale based on probabilities to a frequency scale based on historical failures. Assumptions made during the original assessment may have been confirmed or refuted through the data. The firm’s (or patients’) risk tolerance may have changed, or the internal or external context may have evolved, calling previous risk acceptance decisions into question. Finally, the QRM program might have reached a more mature state such that the original risk assessment no longer meets current standards or objectives. In the event the living risk assessment is affected in any way based on the learnings from the event (for event-driven risk review) or over time (for periodic risk reviews, the risk assessment and associated documentation should be updated to reflect the current state of the art. Incorporating these practices and perspectives of risk review will enhance risk maturity and better protect the patient.
8.6 Maturity with regard to risk communication

As discussed in the context of the nuclear industries in Chapter Six, communication is an art not to be taken lightly; this is particularly true of risk communication, where sensitive technical information may be misinterpreted if not communicated appropriately. ICH Q9 defines risk communication as “the sharing of information about risk and risk management between the decision maker and other stakeholders,” noting:

“The output/result of the quality risk management process should be appropriately communicated and documented… Communications might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.” (45)

There is little guidance offered in ICH Q9 regarding what, specifically, needs to be communicated, to whom, and for what purpose. To answer these question, other sources must be evaluated.

Fischhoff, Brewer, and Downs describe three objectives of risk communication: to share information, to change beliefs, and to change behaviors. (151) Based on the definition of risk communication offered in ICH Q9, it appears that the first of the objectives was considered critical to QRM; the other two objectives are not addressed. Companies mature in QRM, however,
recognize that these goals are not mutually exclusive. Informing people about risks without providing sufficient context to enable them to make their own decisions and act accordingly is sure to be ineffective. Where included context is weak or absent, the recipients of the risk communication will apply their own context—their values, belief systems, risk tolerance, and heuristics. This may blur the intent of the message and have unintentional, negative results.

8.6.1 Understanding stakeholders

As counseled by the NRC in Chapter Six, the first step in effective risk communication is to determine the objective of the communication—to share information, change beliefs, or change behaviors (or a combination of these). The stakeholders must then be identified, and their risk perceptions, risk tolerances, and existing knowledge evaluated. These stakeholders will be the recipients of the risk communication, and may include individuals both internal and external to the company, such as:

- Internal stakeholders
  - Decision makers and leadership
  - Operators, analysts, and specialists
  - Personnel from other manufacturing sites
- External stakeholders
  - Suppliers, service providers, and partners
  - Regulators
  - Public/shareholders
  - Physicians, pharmacists, or other healthcare providers
  - Patients and their families
The existing perceptions of risk will vary for each of these stakeholder groups, and may be influenced by key heuristics, such as the “degree of dreadfulness” of the risk\textsuperscript{59} and expert-lay bias. The communicator should take care to diffuse any inflammatory language and avoid overly technical jargon where these heuristics and perceptions might be at play.

Communicating risk to internal and external stakeholders may also fulfill additional objectives that are worth mentioning here. External risk communication often fulfills commitments to these parties. For example, contractual obligations with third party partners may require communication of significant known or anticipated issues. Regulatory bodies may have explicit or implicit requirements to communicate certain information within certain timeframes. Healthcare providers might need additional information regarding the drug or course of treatment in order to best support their patients. And of course, patients and their families have a right to understand the risks associated with their care. Risk communication to internal stakeholders, on the other hand, is a critical form of knowledge management, offering opportunities for improvement and risk avoidance. One delegate at the June 2017 PDA QRM for Manufacturing Systems workshop summarized this function of risk communication with a relevant anecdote, explaining how his site had been working for several months to solve a persistent manufacturing problem. At a company party, he met a colleague who worked at a sister site that employed a similar technology platform, and shared his challenge. The colleague had experienced a similar issue and described the solution his site had implemented, which led to a longer conversation between the two parties. As it turned

\textsuperscript{59} This researcher recalls viewing a direct-to-consumer television advertisement that disclosed a known side effect of the drug: “urgent diarrhea with fainting”—quite a dreadful and embarrassing side effect in her opinion. It would have been interesting and helpful to have the prevalence of that particular side effect disclosed in the advertisement.
out, the delegate noted, both sites were solving the same problems over and over and were never aware of the shared experience.

Vesper describes important considerations for mature, successful risk communication in his article “Q9 + Ten Years: Examining Risk Communication.” These include building transparency and trust, establishing credibility, and communicating the big picture, among others. With regard to transparency, trust, and credibility, Vesper explains:

“One of the most important elements in risk assessment and risk management is the credibility – the trustworthiness and competence, as perceived by the stakeholders – of those involved. If the stakeholders do not have confidence in those conducting, managing, or sponsoring the activities, the stakeholders may demand higher levels of control or decide to accept only the lowest levels of risk. Conversely, if there is trust, the stakeholders may be willing to accept more risk. Open, honest, two-way communication between all the stakeholders is essential when working to assess and manage risks.” (152)

Vesper also recommends the use of visual aids, such as heat maps and Pareto diagrams in risk communication, as these can help position the risk information in a broad context. (127) For example, where several risks have been found to be unacceptable and are being communicated to decision makers, providing a diagram to show that these unacceptable risks are but a small portion of all assessed risks may temper any immediate emotional response and enable a more fruitful discussion on next steps. In addition, visual aids of risk communication can be employed on a continuous basis, using icons to highlight hazards to users. (153) In the pharmaceutical and
biopharmaceutical industries, such icons may be embedded within batch records or standard operating procedures to communicate risks associated with the process described in the document.

Companies mature in risk communication will identify their stakeholders and take time to understand their interests and perceptions. Trust and credibility will be established and maintained through frequent, transparent communication of risk information. These companies see internal risk communication as a form of knowledge management, and acknowledge their obligation to external stakeholders through risk communication.

8.6.2 Planning for risk communication

The nuclear industry has embraced planning as key to successfully risk communication, and avails itself of the documentation of thoughtfully constructed plans for transmitting risk information to stakeholders in an organized and controlled manner. Pharmaceutical and biopharmaceutical companies seeking to increase their risk maturity might likewise develop such plans, which may include information such as:

- Groups, roles, or individuals responsible for initiating communication,
- Groups, roles, or individuals responsible for receiving communication (stakeholders),
- Groups, roles, or individuals responsible for reviewing messages prior to communication (e.g. medical, legal, or public relations experts for external communication)
- The nature of the communication (e.g. the types of information to be communicated),
- The method of communication (e.g. meetings, email, formal report distribution), and
- A mechanism to document that the communication has taken place (e.g. meeting minutes, printed email)
Table 8-27 offers an example internal risk communication plan that may help firms increase their risk maturity.

A risk communication plan can be valuable in many situations, as it informs individuals of the expectations for communicating certain types of QRM information, helping build a culture of transparency. However, it is reasonable to expect certain situations to arise that are not covered by a communication plan. For example, Krivkovich and Levy claim that “the most effective risk management we have observed act quickly to move risk issues up the chain of command as they emerge, breaking through rigid governance mechanisms to get the right experts involved whether or not…they sit on a formal risk-management committee.” (154)
Table 8-27: Example of a risk communication plan for internal stakeholders

<table>
<thead>
<tr>
<th>QRM Activity</th>
<th>What needs to be communicated</th>
<th>Communicator</th>
<th>Recipient</th>
<th>Format</th>
<th>When to communicate</th>
</tr>
</thead>
</table>
| QRM Plan     | • Objectives  
• Roles and responsibilities  
• Activities and timing | Head of QRM | • Leadership (decision makers)  
• System/ Process Owners  
• Facilitators  
• Subject Matter Experts | • Circulation of approved QRM Plan  
• Presentations | • Upon approval of the plan  
• Upon changes to the plan  
• Upon completion of activities within the plan |
| QRM Initiation | • Risk question/objective and scope  
• Team membership  
• Target timeframe for completion | System/ Process Owner | • Facilitators  
• Subject Matter Experts  
• Leadership (decision makers) | • Circulation of approved risk assessment request  
• Email, phone, etc. | • During planning of the risk assessment request  
• Upon approval of the risk assessment request |
| Risk Assessment | • Unacceptable risks  
• Recommended control measures that will require resources not at the disposal of the team | System/Process Owner | • Leadership (decision makers)  
• Internal customers (e.g. functional groups that may be affected by the unacceptable risk or be involved in implementation of the risk controls) | • Presentations  
• Email, phone, etc. | • Upon completion of the risk assessment, prior to finalization of the interim report |
| Risk Control | • Unacceptable residual risks  
• Risk acceptance decisions | System/ Process Owner | • Leadership (decision makers)  
• Subject matter experts | • Circulation of final report  
• Presentations  
• Email, phone, etc. | • Upon completion of risk control |
| Risk Review | • Outcomes of risk review | System/Process Owner | • Leadership (decision makers) | • Presentations  
• Email, phone, etc. | • Upon completion of the risk review |
| Ad Hoc | • Realized risks  
• Newly identified risks | Person who identified the risk | • System/Process Owner  
• Leadership (decision makers) | • Email, phone, etc. | • As soon as possible following identification |

60 Portions of this plan were previously constructed by the researcher during her work with the PDA QRM Task Force and published in PDA Technical Report No. 54-5. (223)
8.7 An optimized QRM lifecycle

Once the ideal state of QRM was defined, the researcher recognized a key point—that the QRM lifecycle as proposed by ICH Q9 did not seem sufficient to enable the ideal state to be achieved. Being that the ideal state was defined as a synergy of techniques from multiple authoritative documents (including ICH Q9, ISO 14971, and ISO 31000) as well as learnings for industries with a history of excellence in risk management, it follows that the QRM lifecycle would need to be revisited to incorporate learnings from each of these sources. Indeed, the quality system-centric ICH Q9, product-centric ISO 14971, and business-centric ISO 31000 are simultaneously complementary and different, each having advantages over the other. To maximize the value that arise from a QRM mindset and associated activities, these lifecycles must be synthesized to yield an optimal lifecycle.

An important first step, described in ISO 31000, is to establish both the internal and external context under which QRM will be performed. (15) The approach taken, and the risk tolerance used, should be founded in an understanding of patients being served, the regulatory climate, and business considerations such as the availability of life-saving product and their vulnerability to shortage. This context will inform QRM strategies, such which activities should be prioritized for QRM and the risk tolerance that would be most appropriate given the circumstances. Therefore, an optimized QRM lifecycle would certainly begin with this critical step.

Once the context has been understood and a related strategy has been established, the QRM process should be initiated and then continue with risk assessment, broken down
into three sub-steps of risk identification, risk analysis, and risk evaluation. A risk
control option analysis would follow, to plan for risk reduction.

Based on the length of time that may pass between the identification of the risk control
strategy and its implementation, an interim report would be written. This report
documents the QRM efforts up to that point, including the applicable internal and
external context, the QRM initiation, the risk assessment, and the risk control strategy.
Approval of this report serves as a gating mechanism to reinforce ownership and
accountability, and triggers the population of the risk register.

The lifecycle would continue with the risk control phase, which would consist of four
separate steps: risk reduction, evaluation of new or changed risks, residual risk
evaluation, and residual risk acceptance. Risk reduction entails the implementation of
the risk control strategy. Once risk reduction is complete, the new/current state is
evaluated for new risks or changes to existing risks, which facilitate the calculation and
evaluation of the residual risk. Finally, the residual risk is evaluated (for both individual
risks and the risk portfolio as a whole), and a decision as to acceptability is made based
on the risk tolerance.

A final report is then written to summarize the QRM lifecycle to this point, including
the risk assessment and risk control activities and outcomes. This would also detail the
outcomes of the risk-based approach to identify the periodic risk review interval.

Risk review occurs at the frequency defined by the periodic review interval, as well as
when triggered by an event within the quality system. The risk review is intended not
only to incorporate lifecycle data back into the QRM process but also as an opportunity
to augment the QRM efforts based on new knowledge (of both the topic assessed and of risk management in general). Throughout the lifecycle, risk communication occurs according to the Risk Communication Plan.

The optimized QRM lifecycle, as described above, is illustrated in Figure 8-L. In this way, ICH Q9, ISO 14971, and ISO 31000 are synthesized with lessons from multiple industries to capitalize on best practices and engender a holistic risk culture.
Figure 8-L: Optimized Quality Risk Management Lifecycle
This chapter outlined how the QRM process can be performed effectively to manage risk to the patient, including the living risk assessment library, QRM initiation, risk assessment, risk control, risk review, and risk communication. Chapter Nine aims to characterize maturity with regard to QRM governance—the leadership, oversight, and accountability associated with a QRM program.
Chapter Nine: What QRM Maturity Looks Like - Governance

This chapter marks the third and final pillar of effective QRM—governance. Governance plays a critical role in managing risk to the patient, ensuring QRM activities are as effective as possible. Governance has as many definitions as there are sources. Merriam-Webster provides the mundane and grammatical definition of “government.” (155) The Business Dictionary offers an explanation with a bit of context:

“[the] establishment of policies, and continuous monitoring of their proper implementation, by the members of the governing body of an organization. It includes the mechanisms required to balance the powers of the members (with the associated accountability), and their primary duty of enhancing the prosperity and viability of the organization.” (156)

The International Risk Governance Council\(^\text{61}\) offers definitions of governance and risk governance: “Governance refers to the actions, processes, traditions and institutions by which authority is exercised and decisions are taken and implemented. Risk governance applies the principles of good governance to the identification, assessment, management and communication of risks.” (157)

\(^{61}\) Despite the enticing name for this organization, the risk governance framework developed and promoted by the International Risk Governance Council is closer to the risk management processes and lifecycle from ICH Q9, ISO 31000, and ISO 14971 than a governance structure over risk management. As a result, the utility of this organization’s work to the research described in this thesis is limited to these definitions only.
For the purposes of this thesis, the researcher proposes the following operational definition of governance with regard to QRM:

*QRM governance is the set of organizational policies, practices, and norms necessary to ensure QRM is performed effectively.*

This chapter begins with a discussion of the purpose of governance in a QRM context. A discussion of the infrastructure and governance processes needed to successfully execute QRM follows. The chapter continues to briefly describe the content of a mature QRM plan, and finishes with a discussion of metrics and key performance indicators for QRM.

**9.1 The role of governance in QRM**

All programs need law and order. Established governance structures and processes ensure there is a level of oversight and accountability for QRM, and that its principles and practices are widely and effectively deployed. In a typical organization, senior management serves as the governing body, tasked with defining policies and ensuring they are followed as intended. Many regulatory standards make the link between senior management and governance. For example, the EU GMPs point out:

“The attainment of [product quality] is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company... To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System incorporating Good Manufacturing Practice and Quality Risk Management.” (158)
ICH Q10 notes that “senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives, and that roles, responsibilities, and authorities are defined, communicated, and implemented throughout the company.” (52) ISO 14971 prescribes that “top management shall… review the suitability of the risk management process at planned intervals to ensure continuing effectiveness of the risk management process and document any decisions and actions taken.” (101) In addition, ISO 9001, *Quality management systems*, requires that

“top management … provide evidence of its commitment to the development and implementation of the quality management system and continually improving its effectiveness by communicating to the organization the importance of meeting customer as well as statutory and regulatory requirements, establishing the quality policy, ensuring that quality objectives are established, conducting management reviews, and ensuring the availability of resources.” (159)

In their article devoted to the role of senior leadership in QRM, Richter and Haddad state that “…senior leadership must empower the organization to implement the QRM program and obtain support throughout the company to bring the program to realization.” (160) Within a mature QRM program, the purpose of governance includes:

- Establishing and maintaining the appropriate infrastructure, including policies, procedures, and personnel
- Overseeing the QRM program and its deliverables
• Setting strategic direction for QRM and planning work to support it
• Measuring the performance of QRM (161)

Each of these is discussed in detail in the remainder of this chapter.

Three-quarters of the experts interviewed in the Phase 3 research cited management commitment as the one key thing that secures success or failure in QRM. (125) (129) (130) (132) (134) (142) (144) (162) (163) A study of risk management professionals from a variety of industries, conducted by the Harvard Business Review, echoed this sentiment, with an overwhelming majority of respondents citing the “tone at the top” as critical to establishing effective risk management. (164) Unfortunately, as discussed in Chapter Five, the current maturity level of industry with regard to QRM governance is rather low. Bishop McFarland offers her opinion as to why:

“The primary challenge that exists, from my perspective, is the lack of leadership within our industry. This is to say, there are individuals that are running firms; however, there is, based on my experience, a lack of leading. Organizations are still very much focused on metrics and compliance. This ‘tunnel vision’ approach to leadership fails to acknowledge the value of the culture of an organization. Without top management engaged with the quality culture of their organization and without a true intent of changing it, they will not move toward achieving the benefits of Q9 and Q10 simply because they will not be interested in what the outcome of those guidance documents represent: an exploration of uncertainty. Leadership may appear to be risk averse but this is not true... they are not risk averse, they are uncertainty averse. Risk
management has the potential to expose uncertainty but often the [management] culture interrupts…this very critical role.” (134)

In this quote, Bishop McFarland alludes to the potential impact on risk maturity that may be realized through incomplete management commitment—the dedication of senior management to the conduct of QRM and the consistency of their words and actions to that dedication. The expert interviews, philosophical dialogues, and the researcher’s own experience show evidence of a lack of management commitment at companies with immature QRM programs. This often manifests as a disconnect between senior management’s vernacular and the fundamental principles of QRM. For example, throughout the philosophical dialogues for the Phase 2 and 3 research, the researcher noted several “catch phrases” that seem to have become ubiquitous with senior leaders of pharmaceutical and biopharmaceutical companies. These include:

- “Risk it out,” meant to communicate that QRM should be used to justify a reduction in requirements like sampling or testing
- “There’s no risk in <x>,” meant to communicate that QRM would be useless in the specific situation
- “[We performed] a risk assessment to justify,” meant to communicate that the risk assessment would be reverse engineered to support a pre-determined outcome (as discussed in Chapter Eight with respect to risk questions)

The use of these phrases implies a lack of knowledge of QRM and quality principles at the senior management level, a situation to be remedied through the role-based leadership training described in Chapter Seven. In addition, because personnel often take their cue from their management, these sorts of catch phrases can be damaging the risk culture of the organization.
In addition, there are often gaps between senior management’s espoused values for QRM and their actions. This was most often mentioned by conference delegates in the context of resourcing QRM activities—when resources are in short supply, those that are earmarked for supporting QRM are often redirected towards more urgent matters. This phenomenon is not unique to QRM, nor the pharmaceutical and biopharmaceutical industries, as illustrated by Srinivasan and Kurey in their Harvard Business Review article: “Even when executives have the best intentions, there are often gaps between what they say and what they do. As a result, employees get mixed messages about whether quality is truly important. Company leaders must first buy into quality improvement initiatives and clearly demonstrate their own personal commitment to this effort to employees.”

A strong portfolio of governance policies and processes can minimize the impact of these mixed signals from management by ensuring that risk-centric behaviors are exhibited at a defined frequency and understood across the organization. In addition, senior management may also evolve their own thinking and level of QRM knowledge by following the governance models they, themselves, have established. In this way, governance offers stability and focus to organization as it increases its level of risk maturity.

9.2 Establishing QRM infrastructure

One purpose of QRM governance is to establish the appropriate infrastructure to enable the organization to perform QRM effectively. Such infrastructure consists of

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62 The irony of this is not lost on the researcher, nor the conference delegates who participated in the philosophical dialogues. Though QRM is the very thing that can prevent quality crises from occurring, quality crises often limit the organization from performing QRM. This cycle is very difficult to break, particularly in the traditional “fire-fighting” cultures described in Chapter Seven.
documents (policies and procedures) as well as human resources. This section describes the characteristics of a mature QRM infrastructure, designed to better enable QRM and protect the patient.

Pharmaceutical and biopharmaceutical companies are familiar with the use of documents to guide everyday operations; all cGMP regulations worldwide require procedures to be written and followed. Industry executes these requirements in a variety of ways. For example, some companies elect to have different “levels” of documents depending on the scope and intent; these may include, listed from broad application to specific application, policies, standards, global operating procedures that apply to all sites within a company, and standard operating procedure (SOPs) that apply to a single site or department within a site. Other companies may elect to only use SOPs to govern their cGMP activities. Regardless of such document hierarchies, the content to be described for QRM remains the same.

The QRM benchmarking survey (discussed in Chapter Five) found that at least 90% of the respondents’ companies currently have a document that describes the use of QRM, with at least 86% of those complying with ICH Q9. What is not clear from the benchmarking survey is whether these documents enable risk maturity and effectiveness as well. The minimum content for an effective primary QRM document includes:

- Purpose and scope of the document, including a list of which product lifecycle phases and quality system elements are within scope of QRM
- Roles and responsibilities for QRM, including the training requirements for each role
- Principles of QRM, including statements of and related program design to ensure:
  - QRM cannot be used to attempt to justify not following applicable law
  - QRM formality should be proportional to the risk of what is evaluated through QRM
  - QRM must be based on scientific evidence, but not a surrogate for science in decision-making
  - QRM must ultimately link to the patient
- Description of when and how QRM should be initiated
- Description of the minimum requirements for risk assessment, including the distinction between living and ad hoc risk assessments
- List of risk tools that may be employed
- Description of risk tolerance for each applicable product or product family and associated levels (where used)
- Requirements for risk control and residual risk acceptance, based on the risk tolerance(s)
- When and how risk review should be undertaken
- When, how, and to whom risk communication should occur, including the urgent escalation of critical risks to decision makers
- Descriptions of governance processes

Based on the current and desired levels of risk maturity of the organization, additional procedures may need to be installed to guide the organization. For example, the creation of a guidance document or whitepaper to describe best practices for risk assessment, risk control, risk review, and risk communication (using the learning from Chapter Eight) may be advisable for companies with a moderate level of maturity who seeks to gain efficiencies and expand knowledge. For companies will low levels of maturity, it is advisable to standardize practice of risk tools through the creation of
procedures, to ensure consistency of execution and to augment the training facilitators have received, until such time as the procedures are no longer necessary.63 (138)

The other aspect of QRM infrastructure to be established through governance is the personnel who will work within the program. As discussed in the benchmarking survey in Chapter Five, there is a widespread misconception in the pharmaceutical and biopharmaceutical industries that the quality unit or department “owns” QRM. While the quality unit has an important role to play, the actors in a QRM program may come from any number of functional groups. After all, “siloed approaches to risk management create dangerous blind spots for business.” (166) In companies with mature QRM programs product quality and patient safety risks are ultimately owned by those who own the product. Who else should be more invested in managing risk to the patient? These individuals are called System or Process Owners and often work within manufacturing functions. (138) In owning the risks associated with their portion of product manufacturing (such as solution preparation, component preparation, upstream processing, or fill/finish), the System or Process Owners carries the following responsibilities under the QRM program:

- Initiates the QRM process for his or her scope of responsibility (i.e. system or process)
- Participates on the risk team for all applicable risk assessments
- Directs implementation of mitigation activities
- Authors risk reports
- Initiates and participates in all applicable risk reviews
- Communicates risks to the appropriate stakeholders

63It is the researcher’s opinion that SOPs on risk tools should never become irrelevant, provided they are not so restrictive to prevent customized tool creation or thoughtfully conceived and appropriately documented alteration. To better manage risk to the patient, consistency is key.
• Ultimately accountable for the application of QRM principles and practices for his or her scope of responsibility

While System/Process Owners are accountable for the risks associated with their area of responsibility, they are not accountable for the functioning of the overarching QRM process as a whole. In mature QRM programs, this privilege is granted to the Head of QRM. This role is likely to align functionally within quality, and preferably reports into the head of quality for the site or organization. This allows the individual a direct line of access to senior management and associated governance forums. It also appears, based on philosophical dialogues, that there may be a correlation between the number of “full time equivalent” (FTE) resources dedicated to QRM and the organization’s risk maturity. For example, QRM warrants at least one FTE at most companies. Larger sites or campuses may require multiple FTEs to fully support the QRM program, while small companies may not be able to financially justify a fully dedicated person and may instead allocate a fraction of an FTE to the role. Regardless of resource allocation, the responsibilities of the Head of QRM (or QRM department) include:

• Accountable for the design and deployment of the QRM program
• Authors policies and procedures
• Oversees QRM training and education
• Provide ongoing mentoring and coaching of personnel on QRM principles and practices
• Leads QRM governance processes (refer to section 9.3)

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64 In the US, one FTE is generally equivalent to 40 hours of work per week, as it assumes that one person would be solely dedicated to the work topic, with the average workweek spanning 40 hours.
In addition to the Head of QRM and System/Process Owners, QRM governance requires the identification of a Facilitator role. These are highly trained QRM experts (refer to Chapter Seven for a discussion of the applicable educational program) who are responsible for leading risk assessments using particular risk tools and serving as QRM SMEs for the organization. Companies mature in QRM resource facilitators from a variety of functional groups, who commit a portion of their time (perhaps 20%) to QRM. This model ensures that QRM knowledge is spread throughout the company in a way that enhances risk culture and maturity. (138)

QRM governance must also define roles and responsibilities for Subject Matter Experts (SMEs) and the quality unit. SMEs are those individuals with expertise in a particular topic who will share their knowledge and data analyses in risk assessments and risk reviews, as described in Chapter Eight. While personnel from the quality unit may serve as experts in quality and compliance as an input into a risk assessment or review, an independent quality professional should also be required to ensure the output of these align with applicable internal and external quality standards.

Finally, it is a purpose of governance to not only defines roles and responsibilities for the QRM program, but also to ensure that the individuals who fulfill these roles to be aware of it. Companies with immature QRM programs often have requirements for, for example, System/Process Owners or SMEs, but are not clear on who fills these roles, often because the roles do not directly correlate with job titles. (128) This can lead to quite a few false-starts and much finger-pointing. All System or Process Owners, Facilitators, and SMEs should be aware of their role in QRM and should have the associated responsibilities listed in his or her job description. This will ensure that accountability for QRM is directly and explicitly associated outlined.
9.3 Overseeing the QRM program

The second purpose of QRM governance is to oversee the QRM program, including ensuring that decision makers and senior leadership have a direct line of sight to risks that may affect product quality and patient safety. This is accomplished, in part, through risk communication, as described in Chapter Eight, which should complete governance processes and forums that focus specifically on QRM. In an effective QRM program, these should cover both tactical risks, such as those identified through living or ad hoc risk assessments, and more strategic or systemic quality risks. There are two such processes that can enable this holistic view when performed in parallel: the risk register, which is designed for tactical risks, and the quality risk profile, intended for strategic risks. Figure 9-A illustrate these QRM governance processes, which merge as part of overall quality management to be reviewed during Quality Management Review.

![Figure 9-A: Parallel governance processes for QRM](image_url)
Though many pharmaceutical and biopharmaceutical companies perceive the risk register as a regulatory requirement, the origins the risk register as a QRM governance tool are unclear. (138) (128) ICH Q9 does not mention a risk register in any form, nor is a risk register explicitly discussed in any authoritative document in the US or EU. The mention of the use of such a register for QRM can be traced back to a question and answer webpage from the Medicines and Health Product Regulatory Agency (MHRA) in the United Kingdom, posted in 2010. (62) (167) In response to the frequently asked question (FAQ) “should site have a formal risk register and management process?”, the MHRA responded:

“Yes, a risk register (or equivalent title document) should list and track all key risks as perceived by the organisation and summarise how these have been mitigated. There should be clear reference to risk assessments and indeed a list of risk assessments conducted should be included or linked to the register. A management process should be in place to review risk management – this may be incorporated into the quality management review process.”65 (168)

Irrespective of the regulatory basis for the risk register as a requirement of QRM, it remains a vital governance tool to inform decision makers of critical risks identified through QRM and for tracking risk reduction and mitigation activities.

65 MHRA has since removed any reference to the risk register from its webpage. As of May 1, 2017, the MHRA FAQs on Risk Management remained available through the UK’s National Archives at: http://webarchive.nationalarchives.gov.uk/20120913151405/http://mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandard/GoodManufacturingPractice/FAQ/QualityRiskManagement/index.htm. However, as of this writing, this webpage is no longer available at this link, and a search of the archives for these FAQs yielded no results. The FAQs remain available through International Pharmaceutical Quality (IPQ), however, at the link provided in the citation.
Living and ad hoc risk assessments serves as inputs into the risk register, which compiles selected information from each risk assessment into a single list, serving as a quality risk “executive summary” of sorts. Information is usually filtered prior to transcription into the risk register; for example, some firms may choose to log only those risks that exceed a given risk tolerance, while others may log all risks that are being mitigated, regardless of level. Typical information included in the risk register is:

- Hazard/Risk
- Risk level (e.g. RPN)
- Source (e.g. risk assessment number and title)
- Risk owner (e.g. applicable System/Process Owner)
- Mitigation activities, responsible parties, and target implementation dates
- Risk closure date (e.g. mitigation plan completion date)
- Residual risk level

Some of the experts interviewed for the Phase 3 research indicated that companies mature in QRM would also track those risks that were accepted, including the acceptance rationale, date, and applicable decision maker, to ensure full transparency and accountability. (130) (129) The risk register should be made available to all employees, to increase awareness of critical quality risks throughout the organization. (132) A risk register template, designed to enable enhanced risk maturity, is offered in Appendix II.

Proper QRM governance would include periodic reviews of the risk register by senior management. Figure 9-B illustrates a general process, proposed by the researcher, for maintenance of the risk register.
Living and ad hoc risk assessments

Do any risks exceed the risk tolerance of the organization?

Include applicable risks and associated data in risk register

Risk Register governance forum: review register and update status

Do any risks require escalation?

Communicate risks to applicable stakeholders

No

Yes

Accepted risks

“Close” risk (remove from risk register)

Escalate to Quality Management Review forum

Figure 9-B: Risk register process flow

The Head of QRM (or QRM staff) should be responsible for the construction of the risk register and will serve as the meeting lead for the risk register governance forum—a meeting dedicated to the review of the register contents. The meetings should be conducted frequently, based on the rate at which risks are added to the register and status updates are expected. A typical meeting agenda may include a review of newly populated risks, risks targeted for acceptance (and subsequent removal from the risk register), status updates on the progression of mitigation activities, and a general
discussion on which risks, if any, require escalation to Quality Management Review. In a mature QRM program, escalated risks should meet one or more of the following criteria:

- Risks that place the patient in jeopardy (urgent escalation required)
- Risk control strategy has not been defined
- Risk control strategy is delayed in its implementation
- Interim controls for unacceptable risks have not been defined
- Resources not at the disposable of the risk assessment team are needed (for example, capital for large design projects or resources from outside the site)

Directing these types of risks to broader forums ensures that senior leadership has the information and ability to hold System/Process Owners accountable for reducing risks in their area of responsibility, and can facilitate the removal of obstacles that might prevent risks from being reduced to an acceptable level.

While the risk register ensures that senior leadership is aware of tactical quality risks, strategic risks require a different governance process. In many cases, systemic risks are often not captured through individual living or ad hoc risk assessments, which are based on a specific scope and risk question as discussed in Chapter Eight. Two experts interviewed for the Phase 3 research suggested that these types of risks are captured in a quality risk profile. While these two experts could only cite one instance each of the quality risk profile in use, both proclaimed it a best practice that could help industry advance in risk maturity and fill a potentially significant gap in perspective between “traditional” QRM and the patient. (127) (125) A proposed template, prepared by the researcher, for the quality risk profile is offered in Appendix III.
The primary objective of the quality risk profile is to assess the quality and compliance status of the site or organization through the review of trends and prospective indicators that may represent quality or compliance risks. The quality risk profile builds awareness of site vulnerabilities and their gravity, in an effort to continually improve the quality system and pinpoint those risks that require strategic intervention to reduce to within the organization’s risk tolerance. (125) (127) Unlike the risk register, whose data is created by others and reviewed during the governance forum, the quality risk profile is created by the governing body itself—it should capture all of the things that keep leadership awake at night, or perhaps more appropriately, the things that should keep them awake.

Issues that represent, or have the potential to represent, quality or compliance risks may arise from various sources and contain both reactively and proactively identified risks as illustrated in Figure 9-C.66

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**Figure 9-C: Proactive vs. reactive risks**

66 A modified version of Figure 9-C was created by the researcher for the PDA QRM Task Force and was published in PDA Technical Report No. 54-5, Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems. (256)
Quality and compliance risks are identified using data trends of systems and processes or through subjective assessments of changing conditions. Examples of data feeder streams for the quality risk profile include:

- Site review forums such as metric reviews or Quality Management Review (reactive)
- Deviation/investigation trends that represent a systemic issue within the quality system (reactive)
- Internal audit and external inspection observations and/or comments, either specific to the site (reactive), communicated from other sites in the organization (proactive), or identified through benchmarking exercises with other organizations (proactive)
- Intelligence information regarding potential changes to organizational capability, processes, and regulatory or business requirements (proactive)
- Regulatory and business intelligence information regarding evolving expectations of health authorities and industry best practices (reactive or proactive, depending on the nature of the information)
- Gaps between current processes, technology, and/or infrastructure and industry standards (proactive)

From these data, risks can be identified and populated on the quality risk profile, along with supporting details such the risk owner, type of risk identification (proactive/reactive), type of risk (patient safety/product quality/compliance/other), and applicable quality system element (aligned to ICH Q10). These data can facilitate trending and metrics calculation, as discussed later in this chapter. Each risk is then ranked for likelihood or frequency and severity, and a risk level is calculated. Example ranking criteria for the quality risk profile is offered in Table 9-1: Example severity ranking criteria for the quality risk profile are offered in Table 9-1 and Table 9-2. The
associated risk level is determined by locating the intersection of these two rankings in a simple “9-box” matrix, as shown in Figure 9-D.

**Table 9-1: Example severity ranking criteria for the quality risk profile**

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>Extremely significant impact. Indicative of a systemic issue that permeates multiple aspects of the Quality System. Risk could result in a critical product quality or safety impact to patient/user. Could result in a shortage of a life-saving drug.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderately significant impact. May extend to another aspect of the Quality System, but the impact can be contained. Risk could result in a moderate product quality impact that is unlikely to affect patients. Not likely to result in a shortage of a life-saving drug, or likely to result in a shortage of a non-life-saving drug.</td>
</tr>
<tr>
<td>Minor</td>
<td>Risk has no impact to product quality or patient safety.</td>
</tr>
</tbody>
</table>

**Table 9-2: Example likelihood/frequency ranking criteria for the quality risk profile**

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Criteria</th>
<th>Proactively-identified risks</th>
<th>Reactively-identified risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent/ Likely</td>
<td>Realization (occurrence) of risk is inevitable unless immediate, sweeping reform/mitigation is implemented.</td>
<td>Trend occurred in the past, either in consecutive intervals or with a clear pattern (e.g., seasonal) and/or risk is likely to recur without mitigation.</td>
<td></td>
</tr>
<tr>
<td>Intermittent/ Average</td>
<td>Realization (occurrence) of risk is likely but may be avoided with the implementation of targeted mitigation activities within the site.</td>
<td>Risk may have occurred in the past but in a non-consecutive/sporadic interval and/or risk may recur without mitigation.</td>
<td></td>
</tr>
<tr>
<td>Rare/ Remote</td>
<td>Realization (occurrence) of risk is moderately likely to unlikely; existing Quality System controls expected to restore steady state.</td>
<td>Risk isolated in time and/or highly unlikely to recur.</td>
<td></td>
</tr>
</tbody>
</table>
Figure 9-D: Risk matrix for the quality risk profile

The risk level is used to determine the need for risk reduction, and the QRM process continues, as discussed in Chapter Eight. Vesper applauded the visualization of the quality risk profile in a “heat map” plotted by quality system element. (127) This can show the relative distribution of strategic quality risks by risk level, as well as enable the onlooker to understand which aspects of the quality system are most vulnerable for the organization. An example heat map is provided in Figure 9-E.
Through the application of governance processes covering both strategic and tactical quality risks, the oversight of key risks for the organization and the patients it served can be achieved.

9.4 Setting strategic direction and planning activities to achieve it

The third purpose of QRM governance is to identify a strategy for QRM and develop plans to achieve it. In a company with a mature QRM program the strategy will, of course, be linked to managing risk to the patient, and may also include elements that describe how this will be achieved. The development of a vision and mission for the
QRM program may best articulate the strategy in a form that can energize the organization. For example, a mature QRM program might have the following vision and mission:

**Vision:** To protect the patient through the management of quality risks

**Mission:** To fully understand and manage critical risks to product quality, to integrate risk-based thinking throughout the organization, and to foster a proactive, anticipatory culture in which quality risks are anticipated and avoided.

As discussed in the context of medical device risk management in Chapter Six, the planning of QRM objectives and activities is critical to the realization of a QRM strategy. In addition, a QRM plan can be a valuable communication vehicle to inform the organization of management’s commitment to and intentions for QRM, and how each QRM practitioner’s work relates to these strategic goals. A QRM plan, therefore, must explicitly address strategies, objectives, tactics, and associated activities over a defined timeframe to serve as a guiding light for all things risk. Figure 9-F illustrates the relationship between these critical components of a QRM plan.
The remainder of this section describes the content of a QRM plan as proposed by the researcher that can be used by the pharmaceutical and biopharmaceutical industries to enhance risk maturity and better manage risk to the patient.

**Purpose section**

The purpose section of the QRM Plan should describe the goal and intent of the plan. Depending on the individual firm’s current level of risk maturity, the goals might differ. For example, less mature firms may elect to focus on the development of a QRM process, governance structure, and training, while more mature firms may wish to focus on expanding an existing QRM program to additional aspects of the quality system. This section serves to ground the reader in the primary objectives of QRM over a defined time period.
**Scope**

The scope section should describe the boundaries of the QRM Plan, and should use exclusionary language where necessary to describe elements or areas that are out of scope. This section may include, for example:

- The site or sites to which the QRM Plan applies,
- Products, product lines, and/or systems to which the plan applies,
- Product lifecycle phases to which the plan applies (e.g. development through Phase I, commercial only, etc.),
- Quality system elements included in the plan (e.g. change control, deviation management, etc.)
- Timeframe covered in the plan

It is recommended that the QRM Plan cover a timeframe spanning one to three years, enabling both short-term “quick wins” as well as longer-term strategic objectives to be outlined.

**Roles and responsibilities section**

This section of the QRM plan should outline the roles and responsibilities for those working or interacting with the QRM program. It is recommended that the following roles be addressed in order to align with the ideal QRM program model proposed in this thesis:

- Senior leadership
- Head of QRM
- Facilitators
- System/Process Owners
- Subject Matter Experts (SMEs)
- Quality Unit (QU)

Many firms have experienced success with the use of a Responsibility Assignment (RACI) matrix which maps each role to a given activity according to whether they are Responsible, Accountable, Consulted, and/or Informed. The responsibilities and tactics or activities outlined in this section should directly correlate to the content of the plan; that is, all activities within the plan should be assigned to a specific role, and each responsibility listed should likewise have specific actions associated with it. This practice ensures clarity is provided to both the readers and users of the plan. For example:

**Table 9-3: Example RACI Matrix for QRM Plan**

<table>
<thead>
<tr>
<th>Tactic</th>
<th>Leadership</th>
<th>Head of QRM</th>
<th>Facilitators</th>
<th>System/Process Owners</th>
<th>SMEs</th>
<th>QU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete defined living risk assessments</td>
<td>I</td>
<td>C</td>
<td>R</td>
<td>A</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Integrate QRM principles into quality system</td>
<td>C</td>
<td>A/R</td>
<td>N/A</td>
<td>R</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Establish risk register</td>
<td>I</td>
<td>A/R</td>
<td>N/A</td>
<td>R</td>
<td>C</td>
<td>I</td>
</tr>
<tr>
<td>Establish quality risk profile</td>
<td>I</td>
<td>A/R</td>
<td>N/A</td>
<td>R</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

Strategy mapping and activity list

The bulk of the QRM plan should include a discussion of strategies, objectives, tactics, and activities for the QRM program, as described in the purpose and scope sections.
The objectives and activities defined in the plan will vary according to the level of maturity of the firm’s QRM program, as well as the length of time the QRM program has been in use. The researcher suggests that mature QRM programs might employ a strategy of “implement a robust quality risk management program to better protect the patient.” A resultant QRM plan may be structured as shown in Table 9-4.

Table 9-4: Example strategy mapping for QRM plan as proposed by the researcher

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Tactics</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate risks associated with all critical operations on site</td>
<td>Design ideal living risk assessment library</td>
<td>Define critical operations</td>
</tr>
<tr>
<td></td>
<td>Perform gap analysis between ideal living risk assessment library and risk assessments currently in place</td>
<td>Perform and document gap analysis</td>
</tr>
<tr>
<td></td>
<td>Complete defined living risk assessments</td>
<td>Complete HACCP for warehouse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complete process FMEA for fill/finish operations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complete HACCP for fill/finish facility and equipment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complete process FMEA for solution preparation</td>
</tr>
<tr>
<td>Integrate QRM in the quality system</td>
<td>Integrate QRM into third party management</td>
<td>Develop QRM approach to supplier management</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Develop QRM approach for contract manufacturers</td>
</tr>
<tr>
<td>Understand portfolio of quality risks for the site</td>
<td>Establish quality risk profile</td>
<td>Develop baseline quality risk profile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Develop process to maintain the quality risk profile</td>
</tr>
<tr>
<td></td>
<td>Establish risk register</td>
<td>Develop baseline risk register</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Develop process to maintain the risk register</td>
</tr>
</tbody>
</table>

The activities in the QRM Plan should be prioritized using a risk-based framework, such that all stakeholders will understand the rationale for the cadence of tasks. Such a risk-based prioritization tool might involve the ranking of each activity for the criticality of the topic and the complexity of the effort, as follows:
Table 9-5: Topic criticality ranking criteria, for QRM activity prioritization

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>Topic directly impacts product quality and the health and safety of the patient.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Topic indirectly impacts product quality and the health and safety of the patient.</td>
</tr>
<tr>
<td>Minor</td>
<td>Topic does not impact product quality or the health and safety of the patient.</td>
</tr>
</tbody>
</table>

Table 9-6: Effort complexity ranking criteria, for QRM activity prioritization

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex</td>
<td>Significant resources and expertise required.</td>
</tr>
<tr>
<td>Average</td>
<td>A moderate amount of resources and expertise required.</td>
</tr>
<tr>
<td>Simple</td>
<td>Minimal resources and expertise required.</td>
</tr>
</tbody>
</table>

The intersection of the individual rankings for topic criticality and effort complexity is then located in the prioritization matrix to determine the relative priority of the activity.

Figure 9-G: QRM activity prioritization matrix
The relative priority of each QRM activity can be used, in addition to an analysis of activity interdependencies, critical path identification, and other considerations, to determine an appropriate timeframe for completion. This enables the firm to allocate resources towards the most appropriate activities to enhance QRM maturity and deliver a direct benefit to the patient. An example activity list using the above principles is shown in Table 9-7.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Resources required</th>
<th>Criticality</th>
<th>Complexity</th>
<th>Priority</th>
<th>Target completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete process FMEA for fill/finish operations</td>
<td>As appropriate</td>
<td>Critical</td>
<td>Average</td>
<td>2</td>
<td>Q1, Year 1</td>
</tr>
<tr>
<td>Complete HACCP for fill/finish facility and equipment</td>
<td>As appropriate</td>
<td>Critical</td>
<td>Complex</td>
<td>3</td>
<td>Q2, Year 1</td>
</tr>
<tr>
<td>Develop QRM approach to supplier management</td>
<td>As appropriate</td>
<td>Moderate</td>
<td>Simple</td>
<td>4</td>
<td>Q3, Year 1</td>
</tr>
<tr>
<td>Complete process FMEA for solution preparation</td>
<td>As appropriate</td>
<td>Critical</td>
<td>Simple</td>
<td>1</td>
<td>Q1, Year 1</td>
</tr>
<tr>
<td>Complete HACCP for warehouse</td>
<td>As appropriate</td>
<td>Moderate</td>
<td>Average</td>
<td>5</td>
<td>Q2, Year 2</td>
</tr>
<tr>
<td>Develop baseline quality risk profile</td>
<td>As appropriate</td>
<td>Minor</td>
<td>Average</td>
<td>8</td>
<td>Q4, Year 1</td>
</tr>
</tbody>
</table>

A thoughtfully constructed QRM plan translates the strategy established by leadership into actionable tasks, thereby ensuring the organization remains centered upon the things that matter most—protection of the patient.

### 9.5 Measuring QRM performance

The final function of governance—to measure performance of the QRM program—is one that has confounded risk management experts for some time. Organizations often calculate metrics, a subset of which are christened “key performance indicators” or
KPIs, to evaluate the performance (and changes in performance) of various business and operational measures. Risk management experts at Protiviti note:

“Improved risk measures, metrics, and monitoring integrated with key performance indicator (KPI) reporting facilitates the shift from ‘guessing’ to ‘knowing’ or ‘understanding’ as well as from ‘reacting’ to ‘being prepared’ or ‘proactive’ or ‘forward looking’. These shifts provide evidence of improved risk management over time.” (169)

There are two questions to be answered through the calculation and review of metrics and KPIs: (a) is QRM being performed effectively? and (b) is QRM effective at managing risk to the patient? The first of these questions focuses on whether QRM principles and practices are being implemented in an effective manner; that is, whether the QRM process is being followed in a manner conducive to risk maturity. The second question focuses on measuring whether QRM is achieving its objective—protecting the patient. This second question is notoriously difficult to answer, primarily because truly effective QRM, integrated throughout the quality system, would be seamless. When QRM is properly designed and deployed, there are fewer problems in the organization. Processes are better controlled. There are fewer deviations and associated investigations. Changes are more effective. Reactive CAPA is replaced with proactive risk control. Right-first time efforts abound. While there are obvious challenges with measuring an absence of data; as would be the case when QRM is applied from the start of the product lifecycle, measuring changes in these parameters following the application of QRM can be misleading. Attributing improvement in quality and reliability solely to QRM is riddled with assumption—in many cases, other quality improvement efforts, such as deeper investigations and root cause analyses, more
effective CAPA, human error prevention programs, or technology enhancements may also contribute to improvements. While the establishment of precise metrics to measure the direct impact of QRM on enhancing product quality and patient protection can be a futile endeavor due to the number of variables involved, measuring product quality improvements over time can provide valuable information on the relative influence of QRM in managing risk to the patient. A measure of this kind is therefore critical to any set of metrics for QRM. (170)

The second question to be answered through metrics and KPIs, “is QRM being performed effectively?,” is perhaps less noble than measuring patient protection. However, in a well-designed QRM program, it is equally important to evaluate performance related to program implementation as program impact. Many organizations, unfortunately, fail to establish meaningful metrics—those that provide a perspective on performance that highlights vulnerabilities, opportunities, and success. A majority of industry conference delegates involved in philosophical dialogues with the researcher mentioned only one metric for QRM at their companies—the number of risk assessments performed. This metric is weak for a number of reasons. First, it fails to measure QRM performance, focused only on the volume of activity. Second, as discussed in Chapter Eight, the number of risk assessments should reflect the strategic design of the living risk assessment library and therefore should be largely predictable. Finally, conclusions based solely upon a single metric are likely to be myopic, failing to provide decision makers and other stakeholders with the information needed to make strategic decisions regarding the QRM program.
Instead, the researcher recommends that a small portfolio of metrics be established and measured on a periodic (monthly) basis. In order to ensure a balanced approach, QRM metrics should:

1. Measure activities in each key phase of the QRM lifecycle (risk assessment, risk control, risk review, and risk communication) as well as programmatic elements (infrastructure and risk maturity)
2. Include a mix of leading (predictive of future success) and lagging (reflective on past performance) indicators
3. Include a mix of trend (measurement over time to understand organizational progress) and target (measurement over time with a defined goal) models
4. Provide meaningful information that can enable decision making by multiple stakeholder groups (e.g. leadership, middle management, QRM practitioners)
5. Be easily calculated; data required to complete the metrics should be readily available and should not pose an undue burden on those who report data nor those who compile the metrics (171) (172) (173) (174)

The first objective of the development of a meaningful set of metrics is to ensure that all QRM lifecycle phases—risk assessment, risk control, risk review, and risk communication—are represented. The need for this is clear—the organization must ensure that QRM as a whole is functioning effectively. The inclusion of metrics around QRM infrastructure is critical to ensure that the program is appropriately resourced and that expertise within the organization is proliferating. In addition, a measure of risk maturity is beneficial to evaluate not only what is being done, but how it is being done. Chapter Ten presents a measurement tool for risk maturity developed by the researcher that can be used to calculate associated metrics.

Including both lagging and leading indicators in the metrics set is listed as the second objective. Lagging indicators are the most common form of metrics used in the
pharmaceutical and biopharmaceutical industries, and measure past performance using data gathered from the quality system. While lagging indicators are informative, they are not always predictive of future performance; leading indicators perform that function. Deloitte defines leading indicators as “information that has a predictive quality in that it measures current events highly correlated to the future results or that directly drive future results through cause-and-effect relationships.” Knowledge gained through an analysis of leading metrics can enable course-corrections in real time, to influence future outcomes. Leading indicators are therefore proactive in nature—a fitting perspective for QRM.

The third objective centers upon whether the metric is more conducive to trending or goal setting. Metrics used to set targets, such as a specific percent reduction in quality defects, can mobilize the organization towards a shared objective and influence behaviors accordingly. Where targets are established for the wrong metrics, however, these same attributes can have negative effects; for example, setting a target for a percent reduction in manufacturing deviations may result in under-reporting from personnel who are incentivized more strongly to meet the target than to follow the rules. In these instances, it is wiser to trend the metric over time to see patterns, and working on activities associated with leading metrics to improve future performance.

A common pitfall in metrics creation, as reported in the philosophical dialogues, is the failure to fully understand what the data means; that is, what conclusions can be drawn from the information and whether these conclusions offer insight needed by the organization. As described above, for example, the number of risk assessments performed over time is merely indicative of the amount of work being done. It does not reflect the quality of the work, or whether there are redundancies or inefficiencies
between risk assessments. Nor is it representative of the number of risks identified, which would require a complete understanding of each risk assessment’s scope to fully characterize. Other metrics measure compliance with regulatory standards or company-specific requirements; as discussed in Chapter Five, while compliance is essential, it is only a portion of overall quality. Rather, organizations should focus on measuring and understanding the effectiveness of the work done, regardless of the volume, and whether the patient is better protected as a result.

The fifth and last objective of metrics creation is that the data must be easy to retrieve and the metrics easy to compile. It is far better to spend resources and intellectual energy to manage risk to the patient than to labor over metrics.

A subset of metrics should be selected as KPIs, to be reviewed at the appropriate governance forums. The researcher recommends a maximum of three KPIs for companies of any size, to keep attention focused on the most meaningful performance measures and prevent “paralysis by analysis.” In addition, KPIs should measure the effectiveness of the QRM program and its use, rather than compliance with the program. This will allow stakeholders to make the appropriate linkages with other business and quality objectives, and will reinforce the role of QRM as an enabler of quality systems as per ICH Q10. Finally, the selected KPIs should be those metrics most indicative of the strategic role of QRM—to protect the patient. Table 9-8 offers an example of QRM metrics and KPIs that may be useful in providing insight into the QRM performance of an organization.
This chapter sought to characterize maturity with regard to QRM governance, including the supporting infrastructure, governance mechanisms, QRM plan, and metrics and KPIs. Chapter Ten will synthesize the learnings from the complete research effort through the development of a QRM maturity measurement tool and associated assessment program.
Table 9-8: Example QRM Metrics and KPIs

<table>
<thead>
<tr>
<th>Metric</th>
<th>Provides information on…</th>
<th>Measures…</th>
<th>Type</th>
<th>Trend / Target</th>
<th>QRM lifecycle phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of full-time equivalent dedicated QRM staff67</td>
<td>Organizational progress, leadership commitment</td>
<td>Effectiveness</td>
<td>Leading</td>
<td>Trend</td>
<td>Infrastructure</td>
</tr>
<tr>
<td>Number of qualified facilitators</td>
<td>Organizational progress, leadership commitment</td>
<td>Effectiveness</td>
<td>Leading</td>
<td>Trend</td>
<td>Infrastructure</td>
</tr>
<tr>
<td>Percent of risks identified proactively vs. reactivity (from Quality Risk Profile)</td>
<td>Organizational and cultural progress</td>
<td>Effectiveness</td>
<td>Leading</td>
<td>Trend</td>
<td>Risk Identification</td>
</tr>
<tr>
<td>Number of unacceptable risks (from Quality Risk Profile) categorized by quality system elements</td>
<td>Common pain points, opportunities for improvement</td>
<td>Effectiveness</td>
<td>Lagging</td>
<td>Trend</td>
<td>Risk Identification</td>
</tr>
<tr>
<td>Number of external inspection observations of any type not previously identified on SRP</td>
<td>Level of self-awareness achieved through QRM</td>
<td>Effectiveness</td>
<td>Lagging</td>
<td>Target</td>
<td>Risk Identification</td>
</tr>
<tr>
<td>Percent of risk assessments from QRM Plan completed on time, completed late, or incomplete</td>
<td>Vulnerability of site during inspections</td>
<td>Compliance</td>
<td>Lagging</td>
<td>Target</td>
<td>Risk Assessment</td>
</tr>
<tr>
<td>Number of unacceptable risks with no risk control plan</td>
<td>Passive acceptance of risk through inaction</td>
<td>Compliance</td>
<td>Lagging</td>
<td>Target</td>
<td>Risk Reduction</td>
</tr>
<tr>
<td>Percent of risk control measures/mitigation activities proven effective</td>
<td>Progress in risk control option analysis and implementation</td>
<td>Effectiveness</td>
<td>Lagging</td>
<td>Trend</td>
<td>Risk Reduction</td>
</tr>
<tr>
<td>Percent of periodic risk reviews completed on time</td>
<td>Whether risk assessments reflect current state</td>
<td>Compliance</td>
<td>Lagging</td>
<td>Target</td>
<td>Risk Review</td>
</tr>
<tr>
<td>Number of external inspection or internal self-inspection observations related to QRM program</td>
<td>Whether QRM program and/or use of the program meets regulatory expectations</td>
<td>Compliance</td>
<td>Lagging</td>
<td>Target</td>
<td>All</td>
</tr>
<tr>
<td>Risk register tracking by month – number of high risks, number of medium risks, number of new (opened) risks, number of closed (accepted/mitigated) risks, total number of risks</td>
<td>Effectiveness of risk identification and risk control, organizational progress with regard to the amount of attention paid towards QRM program</td>
<td>Effectiveness</td>
<td>Lagging</td>
<td>Trend</td>
<td>All</td>
</tr>
<tr>
<td>QRM maturity assessment results, over time68</td>
<td>Organizational and cultural progress</td>
<td>Effectiveness</td>
<td>Leading</td>
<td>Trend</td>
<td>All</td>
</tr>
<tr>
<td>Number of quality defects over time68</td>
<td>Influence of QRM in improving product quality and patient protection</td>
<td>Effectiveness</td>
<td>Lagging</td>
<td>Target</td>
<td>All</td>
</tr>
</tbody>
</table>

67 KPIs are shown in yellow.
68 The QRM measurement tool and associated assessment is discussed further in Chapter Ten.
Chapter Ten: Measuring QRM Maturity

With the current state of QRM in the pharmaceutical and biopharmaceutical industries defined, and the future, mature state envisioned, the research effort sought to outline the path towards excellence through the construction of a QRM maturity measurement tool to be used to evaluate the effectiveness of QRM as applied by a drug manufacturing site. As mentioned in Chapter Nine, measuring risk maturity, and the progress towards the ideal state, is a useful means to evaluate efforts towards patient protection and ensure the appropriate oversight of the effectiveness of the QRM program as a whole. This chapter discusses the QRM maturity measurement tool that has been developed by the researcher based on the learning from all phases of the research, which was piloted with several candidate sites from the biopharmaceutical industry to confirm validity and utility. The tool design, usage, benefits, and outcomes of the pilots are discussed. Appendix IV offers the complete measurement tool described in this chapter.

10.1 QRM maturity measurement tool overview

The QRM maturity measurement tool is structured in a similar way to the chapters in Section Three, beginning with an evaluation of the people pillar of QRM, followed by each step in the QRM process, and ending with QRM governance. The tool is therefore organized around headings representative of the three pillars of QRM, with associated sub-headings as delineated in Table 10-1.
Table 10-1: Headings and sub-headings of the QRM maturity measurement tool

<table>
<thead>
<tr>
<th>Heading</th>
<th>Sub-heading</th>
</tr>
</thead>
<tbody>
<tr>
<td>People</td>
<td>Organizational awareness</td>
</tr>
<tr>
<td></td>
<td>QRM expertise</td>
</tr>
<tr>
<td>Risk culture</td>
<td>Application of QRM</td>
</tr>
<tr>
<td></td>
<td>Cultural motivation</td>
</tr>
<tr>
<td></td>
<td>Personnel engagement</td>
</tr>
<tr>
<td></td>
<td>Reward and recognition</td>
</tr>
<tr>
<td>QRM Initiation</td>
<td>Risk question</td>
</tr>
<tr>
<td></td>
<td>Tool selection</td>
</tr>
<tr>
<td></td>
<td>Expert representation</td>
</tr>
<tr>
<td>Risk Assessment</td>
<td>Living risk library</td>
</tr>
<tr>
<td></td>
<td>Risk identification</td>
</tr>
<tr>
<td></td>
<td>Risk analysis</td>
</tr>
<tr>
<td></td>
<td>Risk evaluation</td>
</tr>
<tr>
<td>Risk control</td>
<td>Risk control option analysis</td>
</tr>
<tr>
<td></td>
<td>Risk reduction</td>
</tr>
<tr>
<td></td>
<td>Residual risk appraisal</td>
</tr>
<tr>
<td>Risk review</td>
<td>Risk review structure</td>
</tr>
<tr>
<td></td>
<td>Risk review execution</td>
</tr>
<tr>
<td>Risk communication</td>
<td>Risk communication plan</td>
</tr>
<tr>
<td></td>
<td>Communication of risks</td>
</tr>
<tr>
<td>QRM Infrastructure</td>
<td>Roles and responsibilities</td>
</tr>
<tr>
<td></td>
<td>Dedicated QRM staff</td>
</tr>
<tr>
<td></td>
<td>Qualified facilitators</td>
</tr>
<tr>
<td>Governance</td>
<td>Risk register</td>
</tr>
<tr>
<td></td>
<td>Quality risk profile</td>
</tr>
<tr>
<td></td>
<td>QRM plan</td>
</tr>
<tr>
<td></td>
<td>Metrics and KPIs</td>
</tr>
</tbody>
</table>

Each sub-heading has four levels of criteria that define the level of maturity for that aspect of QRM. Each level has an associated score, ranging from 1 – 4, as shown in Table 10-2.

Learnings from Phase 2 of the research, as discussed in Chapter Five, led the researcher to re-envision the structure of the maturity model for the Phase 3 research to facilitate a more meaningful evaluation of maturity. The first pillar of QRM, “people,” has been separated into two distinct headings—one to capture organizational knowledge of QRM and the other to evaluate risk culture. The second pillar of QRM, “process,” has been...
broken out in the QRM maturity measurement tool to capture each stage of the QRM lifecycle independently. The third “governance” pillar of QRM was also separated into QRM infrastructure and overall governance. This separation enables decision makers to better distinguish strengths and vulnerabilities in the implementation of QRM program than the Phase 2 maturity model and represents an evolution in the researcher’s thinking as the research effort progressed.

Table 10-2: QRM maturity levels and associated scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Maturity Level</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Absent</td>
<td>QRM program element not acknowledged or performed.</td>
</tr>
<tr>
<td>2</td>
<td>Novice</td>
<td>Application of QRM program element is immature.</td>
</tr>
<tr>
<td>3</td>
<td>Intermediate</td>
<td>Application of QRM program element is moderately mature, with room for improvement.</td>
</tr>
<tr>
<td>4</td>
<td>Expert</td>
<td>Application of QRM program element is very mature. Tangible benefits to both the site and patients are realized.</td>
</tr>
</tbody>
</table>

In addition, a level 0 is available for situations in which the site is unaware that such a practice should be acknowledged—that is, the program element represents a blind spot for the organization.

The QRM maturity measurement tool is used through a detailed assessment of the QRM program on site, including both the design of the program, as evidenced by policies and procedures, and application of the program, as evidenced by completed QRM documentation and interviews of site personnel. The mean of the scores for each sub-heading represent the overall maturity score for the related heading, which is then plotted in a chart or “dashboard” to allow for further analysis.
10.2 Recommended use of the QRM maturity measurement tool

10.2.1 Assessment process

The QRM maturity assessment is performed using an evidence-based approach in which randomly-selected samples of QRM documentation are reviewed, and individual QRM practitioners interviewed, to enable the selection of the best-fit maturity score for each sub-heading in the measurement tool. As it not practical (nor valuable) to review every piece of evidence related to the QRM program, the random sampling is presumed to be representative of the population, and therefore allow for characterization of QRM practices as a whole.

The QRM maturity assessment is intended to be performed for a single site within a given pharmaceutical or biopharmaceutical company, rather than the organization as a whole. Because, as seen in Chapter Five, QRM practices can vary within an organization based on factors such as geographical location, assessing risk maturity at the site level provides the most accurate, and actionable, results.

In order to ensure an un-biased evaluation, the QRM maturity assessment should be performed by a party independent of the QRM program and ideally, the site. This may include an independent functional group within the site, as is often the practice for quality self-inspections or internal audits, or an external party such as a consultant may be used. Over time, the site may elect to integrate the maturity assessment into the self-inspection program as an additional means to measure the effectiveness of the quality system through the lens of QRM.
Once identified, the assessor (or assessment team) should begin with a review of the QRM policy, to familiarize themselves with the landscape in which the site has elected to apply QRM. From there, the assessor may request specific documents to review, such as individual procedures, risk assessments, risk reviews, training materials and records, and job descriptions. The assessor may also wish to interview specific individuals regarding their opinions of QRM and how they practice of QRM on site. Table 10-3 suggests various forms of evidence for each sub-heading that may prove useful in the maturity assessment.

With the evidence reviewed, the assessor moves on the selecting the most appropriate maturity score for each sub-heading based on the criteria defined in the measurement tool. Once all scoring is complete, the results are averaged for all sub-headings within a given heading, providing a total of eight individual scores—one each for People, QRM Initiation, Risk Assessment, Risk Control, Risk Review, Risk Communication, QRM Infrastructure, and Governance. These scores are then plotted on a QRM maturity dashboard for further analysis.
Table 10-3: Evidence to review during QRM maturity assessment

<table>
<thead>
<tr>
<th>Heading</th>
<th>Sub-heading</th>
<th>Evidence to review</th>
</tr>
</thead>
<tbody>
<tr>
<td>People</td>
<td>Organization awareness</td>
<td>Training materials, training records, personnel interviews</td>
</tr>
<tr>
<td></td>
<td>QRM expertise</td>
<td>Training materials, training records, personnel interviews</td>
</tr>
<tr>
<td>Risk Culture</td>
<td>All elements</td>
<td>Personnel interviews, QRM plan, risk assessment reports</td>
</tr>
<tr>
<td>QRM Initiation</td>
<td>Risk question</td>
<td>QRM initiation form, risk assessment reports</td>
</tr>
<tr>
<td></td>
<td>Tool selection</td>
<td>SOPs, QRM initiation form, risk assessment reports</td>
</tr>
<tr>
<td></td>
<td>Expert representation</td>
<td>QRM initiation form, risk assessment reports</td>
</tr>
<tr>
<td>Risk Assessment</td>
<td>Living risk library</td>
<td>SOPs, QRM plan</td>
</tr>
<tr>
<td></td>
<td>Risk identification</td>
<td>SOPs, risk assessment reports</td>
</tr>
<tr>
<td></td>
<td>Risk analysis</td>
<td>SOPs, risk assessment reports</td>
</tr>
<tr>
<td></td>
<td>Risk evaluation</td>
<td>SOPs, risk assessment reports</td>
</tr>
<tr>
<td>Risk Control</td>
<td>Risk control option analysis</td>
<td>SOPs, risk assessment reports</td>
</tr>
<tr>
<td></td>
<td>Risk reduction</td>
<td>CAPA lists, risk assessment reports</td>
</tr>
<tr>
<td></td>
<td>Residual risk appraisal</td>
<td>Risk assessment reports</td>
</tr>
<tr>
<td>Risk Review</td>
<td>Risk review structure</td>
<td>SOPs, risk review reports</td>
</tr>
<tr>
<td></td>
<td>Risk review execution</td>
<td>Risk review reports, updated risk assessment reports, meeting minutes</td>
</tr>
<tr>
<td>Risk Communication</td>
<td>Risk communication plan</td>
<td>SOPs, QRM plan, risk communication plan</td>
</tr>
<tr>
<td></td>
<td>Communication of risks</td>
<td>Meeting minutes, email, memorandums, correspondence with external stakeholders</td>
</tr>
<tr>
<td>QRM Infrastructure</td>
<td>Roles and responsibilities</td>
<td>Organizational charts, job descriptions</td>
</tr>
<tr>
<td></td>
<td>Dedicated QRM staff</td>
<td>Organizational charts, job descriptions</td>
</tr>
<tr>
<td></td>
<td>Qualified facilitators</td>
<td>Organizational charts, job descriptions, training plans</td>
</tr>
<tr>
<td>Governance</td>
<td>Risk register</td>
<td>SOPs, risk register</td>
</tr>
<tr>
<td></td>
<td>Quality risk profile</td>
<td>SOPs, quality risk profile</td>
</tr>
<tr>
<td></td>
<td>QRM plan</td>
<td>SOPs, QRM plan</td>
</tr>
<tr>
<td></td>
<td>Metrics and KPIs</td>
<td>Meeting minutes, dashboards</td>
</tr>
</tbody>
</table>
10.2.2 QRM maturity dashboard

The researcher chose a dashboard, rather than a single “rolled-up” maturity score, as the mechanism for analysis. The dashboard takes the form of a radar or “spider” diagram, with each heading plotted as a “spoke” in the diagram and the results of the maturity assessment as points on the chart, as illustrated in Figure 10-A.

![Figure 10-A: Example QRM maturity dashboard](image)

The spider diagram used for the QRM maturity dashboard enables the viewer to see the overall level of QRM maturity, the individual levels of maturity for each pillar of the QRM program, and to explore the balance of maturity to determine where to focus efforts or expand best practices. For example, “risk communication” is shown as an area of relative weakness in the example dashboard from Figure 10-A. However, because the “people” and “QRM infrastructure” headings are more mature, there are opportunities to mobilize the people at the site and leverage the associated infrastructure to improve risk communication within the site. The dashboard therefore serves as a
visual aid to help identify where more mature elements of the QRM can be repurposed to improve maturity in areas that are struggling.

The use of the spider diagram for the QRM maturity dashboard also allows easily comparison of results of the maturity assessment. Figure 10-B, for example, shows how two years of data for the same site can be overlaid to enable the identification of improvements and backslides over time. A similar approach may be used to compare results between sites to evaluate where knowledge and best practices may be transferred from a more mature site to a less mature one.

![Figure 10-B: QRM maturity dashboard illustrating a year-over-year comparison](image)

In this way, the QRM maturity dashboard can provide far more insight into the true level of QRM effectiveness than a simple, overall risk maturity “score.”

### 10.3 Results of the pilots for the QRM maturity measurement tool

As the final inquiry in the research effort, the researcher had the opportunity to pilot the QRM maturity measurement tool and process with two separate biopharmaceutical
companies, for a total of eight sites (seven sites from one company and one site from the second company). Access to each site was granted by senior leadership (specifically, the network Vice President of Quality for one company and the site head of quality for the other). Following the QRM maturity assessment using the measurement tool, each site’s head of quality was queried regarding his or her opinions on the structure of the measurement tool and QRM maturity assessment process. Specifically, they were asked:

- Did you find the QRM maturity assessment valuable?
- Do the results of the QRM maturity assessment accurately reflect your opinions of the maturity of your site’s QRM program?
- Do you plan to take action based on the results of the QRM maturity assessment?

Both companies requested anonymity with regard to this research, and will therefore be referred to as Company A and Company B. All company and site details were relayed to the researcher during the QRM maturity assessments by each site’s Head of Quality.

Company A is a global pharmaceutical firm with a 2016 annual revenue in excess of US $39.2B (33.8B euro) and over 110,000 employees worldwide. The company has divided its business based on product type, with separate business units covering the production of API, small molecule pharmaceuticals, biopharmaceuticals, medical devices, veterinary products, and consumer health products. All seven sites included in the Phase 3 research pilot were operating under the biopharmaceutical arm of the business; however, some of the sites also manufacture medical devices. Company A has a centralized QRM program run by corporate quality that has been tailored by each site to meet their specific needs.
Site 1 within Company A is staffed by an estimated 1200 employees, focused solely on
the manufacture and related support of one sterile biological drug substance. At the
time of the pilot (September 2016), the site had been performing QRM for
approximately five years. Prior to the assessment, the head of quality cited the site’s
primary struggle with QRM as the shift in site culture away from seeing QRM as a box-
ticking exercise necessary for compliance towards one in which the value is fully and
broadly understood. The QRM maturity dashboard for Company A, Site 1 is provided
in Figure 10-C.

![Figure 10-C: Results of QRM maturity measurement tool pilot – Company A, Site 1](image)

Site 2 within Company A has fewer employees than Site 1, totaling an estimated 350
employees within manufacturing and related support functions. Site 2 has an extensive
history of medical device design and manufacturing, and had been performing risk
management in accordance with ISO 14971 for over fifteen years at the time of the
assessment (May 2016). The site’s inclusion of quality risk management principles and
practices in the spirit of ICH Q9 into their overarching risk management program was
more recent, introduced four years prior to the pilot. During the opening meeting for the assessment, the site’s head of quality reported no challenges with his QRM program and anticipated it to be best-in-class. Figure 10-D illustrates the QRM maturity dashboard for Company A, Site 2.

![Figure 10-D: Results of QRM maturity measurement tool pilot – Company A, Site 2](image)

The third pilot site from Company A (referred to as Site 3) employs an estimated 75 people and focuses solely on raw material receipt, testing, and release for other sites in the biopharmaceutical network as well as finished product packaging and distribution. The site had been performing QRM for only one year at the time of the pilot (May 2016) but had established QRM program deployment as the site’s primary quality objective for the prior year. At the start of the assessment, the site’s head of quality acknowledged that the program was young, and was primarily interested in learning the site’s vulnerabilities to enable goal setting for the following calendar year. The QRM maturity dashboard for Company A, Site 3 is shown in Figure 10-E.
Site 4 within Company A employs an estimated 2500 employees and focuses on the production and associated support of four sterile biopharmaceutical drug substances. The QRM program at Site 4 had been in effect for four years at the time of the QRM maturity assessment in February 2016. The site’s head of quality expressed concern in the opening meeting with the number of unacceptable risks reported by the site and the lack of “movement” on those risks—described as either risk reduction or risk acceptance. The QRM maturity dashboard for Site 4 is provided in Figure 10-F.
The fifth pilot site from Company A was new to the company, having been acquired by the large pharmaceutical firm two years prior to the QRM maturity assessment (March 2016). Formerly a small start-up firm, the site had only been applying QRM over the prior six months, largely as a result of the integration efforts into its parent company. The site employs a mere 50 people, and manufactures one aseptically-produced sterile drug substance. The site’s head of quality had no prior experience with QRM himself, and was interested in understanding where the site ranked in QRM maturity in comparison to its peers in the company network. The QRM maturity dashboard for Site 5 is provided in Figure 10-G.
Site 6 of Company A is a rather interesting case, being under consent decree in the US at the time of QRM maturity assessment in October 2016. The site employed approximately 700 employees, an additional 500 external quality consultants, and 30 external consent decree verifiers, to support the production of one sterile biopharmaceutical drug substance at 100% capacity. The site had been performing QRM since the finalization of the consent decree terms six years prior to the pilot. Because the site’s QRM program had been developed by external quality consultants and was cited by the consent decree verifiers as an example of excellence for the rest of the site, the site’s head of quality was exceedingly confident in the opening meeting that the level of risk maturity would be the highest in the company’s network, although

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69 Consent decree is one of the more severe regulatory sanctions available to the FDA, exceeded only by revocation of a drug manufacturing license and physical seizure of drug manufacturing assets. Consent decree entails, among other requirements, the hiring of full time quality consultants to guide reconstruction of the site’s quality system, continuous verification of quality system improvement by a separate consulting body, and disgorgement of profits to FDA from the sale of products manufactured in violation of regulatory requirements.
admitted that the site culture is one of urgent reaction rather than anticipation. Figure 10-I shows the QRM maturity dashboard for Site 6 of Company A.

![QRM Maturity Dashboard](image)

**Figure 10-H: Results of QRM maturity measurement tool pilot – Company A, Site 6**

Site 7 of Company A employs an estimated 120 people to manufacture and support a medical device. Having performed risk management in accordance with ISO 14971 since 2003, the site had incorporated QRM principles four years prior to the QRM maturity assessment date (July 2016). The head of quality at the site appeared mildly disinterested when the assessment commenced, and did not express any concerns with his site’s QRM program. The QRM maturity dashboard for Site 7 of Company A is provided in Figure 10-J.
The final site used in the QRM maturity measurement tool pilot was a single site from Company B. Company B is also a global pharmaceutical firm headquartered in the EU, although the site included in the pilot is located in the US. Company B’s 2016 annual revenue exceeded US $54.2B (46.7B euro) with over 115,000 employees internationally. Similar to Company A, Company B has organized its diversified product portfolio into business units based on product type, including crop science, pharmaceuticals, consumer health, and animal health. The pharmaceutical division in sub-divided into small molecule products and biopharmaceuticals. The site included in this pilot is organized with the biopharmaceutical subdivision.

Site 1 of Company B employs an estimated 2,500 employees to manufacture and support three sterile drugs, including both drug substance and drug product. The site had become interested in QRM following the hiring of a new site head of quality who was particularly interested in the topic. The site had been performing QRM for ten years leading up to the pilot, performed in May 2017. At the start of the maturity
assessment, the new head of quality was distressed by the site’s QRM program when compared with her prior experience, though no specific areas of concern were voiced. Figure 10-K shows the QRM maturity dashboard for Site 1 of Company B.

![Figure 10-K: Results of QRM maturity dashboard for Site 1 of Company B.]

The results of QRM maturity assessment pilots validated the measurement tool as an accurate and constructive means to measure, understand, and improve QRM maturity and effectiveness. All eight heads of quality involved in the pilots agreed that the assessment was valuable, with seven expressing interest in repeating the assessment in one year’s time to gauge improvement. All heads of quality noted that they intend to share the results of the QRM maturity assessment with their staff, some noting that they would include the topic in upcoming town hall-type meetings with all site employees. Seven of eight heads of quality agreed that the QRM maturity measurement tool
accurately reflected their opinions of their site’s QRM effectiveness, with one head of quality (for Company A, Site 6, involved in consent decree activities) acknowledging that he may have been overconfident in the program currently in place at this site. All eight heads of quality noted that they plan to take action to improve the level of QRM maturity within their site based on the outcomes of the measurement tool. The QRM maturity assessment and associated measurement tool are therefore considered to provide an adequate measure of QRM maturity that can help ensure an organization can effectively use QRM to protect the patient.

The QRM maturity measurement tool development and pilots marks the end of the Phase 3 research, and closure of the overarching research effort. The implications of the research, including conclusions, recommendations, and suggested areas for additional research are discussed in the fourth and final section of this thesis.

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70 One quality head (for Company A, Site 2) did not feel that the random sampling of evidence was representative of the population, as it was his opinion that the site was very mature in QRM application. The researcher would like to draw the reader’s attention to the low “governance” score associated with this site (Figure 10-D), as there appears to be a lack of knowledge and oversight of the QRM program at the leadership level. While the researcher cannot definitively state that the head of quality was misinformed regarding the true state of QRM at his site, the results of the QRM maturity assessment indicate that this may be a factor influencing his opinion.
Section Four: Implications of the Research
“When you find yourself in a hole, stop digging.”

- Will Rogers

“Don’t be afraid to take a big step when one is indicated. You can’t cross a chasm in two small steps.”

- David Lloyd George
Chapter Eleven: Focus Areas for Future Research

Perhaps one of the most difficult challenges for any researcher is to stay within the boundaries of the chosen research topic. As the research progresses, ideas abound. The researcher may be left with an unsettling sort of intellectual restlessness when faced with the prospect that those ideas must, in many cases, be left unexplored, if a final body of knowledge were to ever be shared. This researcher, in particular, suffers gravely from this affliction. This chapter aims summarizes the most critical and potentially valuable of these ideas to inspire future researchers.

Future research topic #1

Skeptics within industry require proof, in the form of both statistical correlation and case studies, that QRM will improve product quality and profitability. Future work in QRM should focus on determining whether there is a direct correlation between those companies with mature QRM programs (per the QRM maturity measurement tool) and those with higher quality products, as evidenced by defect rates, recall rates, and other quality metrics. In addition, profitability and cost of goods sold (COGS) should be measured and compared with each firm’s QRM maturity levels. Such an analysis will enable an understanding of the benefits of QRM using tangible outcomes by answer the following questions:

- Do companies with robust, consistent product quality tend to have more mature QRM programs?
- Do companies with more mature QRM programs tend to have more robust product quality?

This will further solidify whether QRM maturity levels are an appropriate leading indicator of patient protection in the form of high quality, more readily available medicinal therapies.

Future research topic #2

Additional research is needed to develop a framework to characterize and improve individual QRM maturity. While the research effort described in this thesis focused on organizational QRM maturity, it did not explore in detail how individuals can contribute to QRM effectiveness. Such a research effort should seek to identify whether there are specific personality types that are more conducive to excellence in QRM, such as introverts or extroverts, or those inclined to be detail-oriented or “big picture” thinkers. Such a research study should also expand upon, and pilot, the education required to cultivate QRM expertise, building upon the model suggested in Chapter Seven of this thesis.

Future research topic #3

While this thesis focused primarily on preventive risk management in the context of accident avoidance, additional research is needed regarding business continuity programs that can accelerate a pharmaceutical manufacturing plant’s return-to-service (or more appropriately, return-to-cGMP) in the event a catastrophe occurs. This is
particularly pressing in light of recent natural disasters that have devastated countries like Puerto Rico, which has a high concentration of drug manufacturing plants.

Future research topic #4

It is this researcher’s opinion that additional research into the application of defense in depth principles and practices, such as those described in Chapter Six in the context of the nuclear power industry, to QRM and cGMP. It would be of particular interest to explore the relationship between defense in depth and Lean, which seeks to eliminate redundancy and idle capacity where defense in depth may seek to add it as a risk control measure.

Future research topic #5

Future research into QRM should aim to expand the existing QRM toolkit with other, proven risk tools, such as the Probabilistic Risk Assessment techniques mentioned in Chapter Six.

The exploration of the above-listed topic through a rigorous academic framework will further enhance knowledge of pharmaceutical quality and enable the patient to be better served.
This thesis has explored the application of quality risk management principles and practices within the pharmaceutical and biopharmaceutical industries, in an effort gauge its effectiveness in managing risk to the patient. Through the use of multiple research methods, the research effort examined the current implementation of quality risk management in these industries and characterized a mature state of QRM implementation, all the while seeking to answer the fundamental question of:

“How can industry recode QRM to better manage risks to the patient?”

12.1 Conclusion

Chapter One of this thesis introduced the reader to the research effort, beginning with an exploration of the context in which patients live—relying on medicines to sustain their life and health, supported by the companies that make these medicines, and hoping that those organizations are working hard to protect them. Protecting patients is simultaneously a privilege and a grave responsibility—a core function of the pharmaceutical and biopharmaceutical industries. After a brief review of the general principles of risk management, Chapter One described how the practice can be applied to medicinal products to ensure patient protection. Different types of risks, intrinsic and extrinsic to the medicinal product, were discussed. While intrinsic risks are relatively well understood and well controlled for the patient, the management of extrinsic risks, particularly quality risks, has been historically neglected by comparison. Recent regulatory modernization efforts have opened the door for the use of risk management in assuring and improving medicinal product quality, thereby better
managing the risk to the patient. The research effort is centered upon exploring whether, and how, this may come to fruition.

Chapter Two of this thesis summarized the initial literature review performed in support of the research effort. The history of risk management in the pharmaceutical and biopharmaceutical industries was reviewed, and the emergent regulatory climate towards one of risk-based, rather than rule-based, quality and compliance was described. The reader was then familiarized with ICH regulation, specifically the four most recent guidelines, ICH Q8(R2), ICH Q9, ICH Q10, and ICH Q11 which grounded the research effort. Finally, a critical review of authoritative industry reports and books on the field of QRM was performed. The literature review described in Chapter Two was just a portion of the overall literature review performed in support of the research.

Chapter Three of this thesis described the researcher’s worldview, the research question, the structure of the research effort, and the research methods to be employed. The researcher discussed her pragmatic worldview and described its fit with the research effort, given the focus on utility rather than ontology. The researcher disclosed her insider perspective as a member of industry, and acknowledged the potential bias that may result as well as the advantages that may be offered. A review of the controls used to conduct the research in alignment with ethical principles and protect research subjects’ privacy was then discussed. The chapter then transitioned to describe the history of the risk question, as the researcher evolved her thinking from the initial research proposal, through the confirmation examination, and ultimately to the writing of the thesis. Finally, the research phases and methods were discussed. The research effort was divided into three phases: the first phase sought to determine whether there is sufficient evidence to confirm that the patient is better protected since the inception.
of quality risk management in the pharmaceutical and biopharmaceutical industries; the
second phase aimed to characterize the extent to which current QRM practices in
industry effectively manage risk to the patient; and the third and final phase sought to
frame what effectiveness and maturity in QRM looks like to improve patient protection.
A mixed methods approach was used throughout the research, consisting of both
qualitative and quantitative research methods including literature review, philosophical
dialogues, benchmarking surveys, data analysis, semi-structured expert interviews, and
pilot case studies.

Chapter Four documented the results of the Phase 1 research, focused on determining
whether the patient has reaped the benefit of better quality products since the advent of
QRM in the pharmaceutical and biopharmaceutical industries, marked by the
publication of ICH Q9. The research used literature review of quality-related medicinal
product recalls in Ireland and the US, which were then analyzed to determine the
presence of any trends that may cast insight into the state of patient protection. In both
represented countries, there was an increasing trend in quality-related recalls over the
time period included in the research. While there may be other variables involved, such
as increased reporting of quality defects or increasing volume of product on the market,
the data did not support a claim that the patient is better protected following the
publication of ICH Q9.

Chapter Five described the results of the Phase 2 research, which explored the ways in
which industry is currently applying QRM and the extent to which these practices
effectively manage risk to the patient. The first research inquiry in Phase 2 explored
whether QRM has improved industry compliance with cGMP, and whether QRM itself
is applied in a compliant manner. This inquiry employed literature review of cGMP-
related warning letters issued by the US FDA and an analysis of the results, which revealed an increasing trend in warning letters over the examined time period. Warning letter citations against QRM practices likewise increased over the same time period, revealing that industry’s compliance with cGMP has not improved since the introduction of quality risk management. In addition, regulators do not seem to have a high level of confidence in the way violative firms have employed QRM, as evidenced by the trend and nature of QRM-related citations seen in the data.

The second research inquiry in Phase 2 sought to identify industry’s current level of risk maturity—envisioned by the researcher as the effectiveness of QRM, the behaviors and motivations of QRM practitioners, and the oversight and accountability of QRM implementation. A benchmarking survey was conducted to reveal these insights. The survey results were flush with learnings, most of which were rather disappointing given the tenure of QRM in the pharmaceutical and biopharmaceutical industries. For example, the overall perspective of the people working with and within QRM is rather apathetic, with pockets of people engaged in QRM but few “true believers” who actively advocate for its use. QRM has not permeated the product lifecycle and quality system to the extent one might expect, and is applied most often in ways that fail to proactively protect the patient. A large proportion of respondents indicated that QRM is often misused, such as to justify current practices or decisions that had already been taken. In addition, ownership and accountability for QRM and the promise it holds for patients is lacking. Philosophical dialogues held during the Phase 2 research indicated a culture of fear, blame, confusion, and excuses. The results of this research inquiry exposed the burning platform that should incite action. The need for the development of a mature model for QRM that can be implemented by pharmaceutical and
biopharmaceutical firms was clear. The researcher forged ahead to address this solution in the Phase 3 research.

Chapter Six described the interim research inquiry that would bridge the Phase 2 and Phase 3. This chapter explored other industries with a history of strong and effective risk management: medical devices, aerospace, and nuclear power. This research inquiry was performed via literature review; the researcher extracted key learnings from the literature that would inform the construction of the mature QRM program desperately needed by industry. These key learnings included:

1. Acknowledge uncertainty associated with the risks being explored and the operating climate in which they manifest themselves. Seek to minimize uncertainty by gaining knowledge and understanding.
2. Define the context in which the risks are identified, analyzed, and controlled. Acknowledge that the context may change and that decisions should be reassessed accordingly.
3. Focus QRM efforts on the product—the most direct link to the patient.
4. Control risks like someone’s life depends on it. Because the patient’s life does.
5. Plan for QRM. Identify gaps impeding a mature state from being realized, and bridge them.
6. Acknowledge the two forms of QRM—continuous QRM and risk-informed decision making. Master both.
7. Culture is key. Learn from mistakes. Avoid making the same mistake twice.
8. Communicate with purpose. Plan for what to communicate, to whom, when. Make sure everyone who needs to know, knows.

Chapter Seven marked the first chapter addressing the Phase 3 research, and defined a mature state of QRM with respect the people working within it. A combination of
literature review, semi-structured expert interviews, and philosophical dialogues were used to define how people can be more effective in applying QRM to protect the patient. The use of role-based QRM was deemed critical, as it ensures that all QRM practitioners, and the organization as a whole, possess a working knowledge of QRM commensurate with their interaction with the program. A high-level framework for developing QRM expertise was proposed by the researcher, seeking to fill a commonly cited gap in the pharmaceutical and biopharmaceutical industries. Finally, the role of risk culture in enabling QRM effectiveness was discussed, and recommendations from the researcher to improve risk culture were offered.

Chapter Eight explored maturity and effectiveness with respect to the QRM process, beginning with a discussion of the strategic creation of a living risk assessment library to ensure that all elements critical to the patient would be included in the QRM program. The chapter went on to discuss best practices for QRM initiation, followed by an introduction to a risk assessment model developed by the researcher to provide a direct line of sight to the patient. The topic of risk control came next, including an examination of best practices to ensure robust risk reduction, residual risk appraisal, and risk acceptance. The chapter then turned to an inquiry into a mature state of risk review, in which knowledge gained is fed back into the QRM process to ensure continued effectiveness of managing risk to the patient. Risk communication was then explored, including an inquiry into stakeholder perception and the creation of a plan to guide risk communication. The chapter closed with a proposed, modified QRM lifecycle to better enable risk maturity and effective patient protection.

Chapter Nine sought to characterize maturity with respect to QRM governance, discussing the importance of leadership commitment and their role in effectively
managing risk to the patient. An effective QRM infrastructure was then proposed, including policies, procedures, and human resources necessary to mobilize the organization to the management of quality risks. Two governance mechanisms were described—the risk register and the quality risk profile—along with process flows and templates created by the researcher. The construction and use of a QRM plan to set and communicate QRM strategy, objectives, tactics, and activities was then described. Finally, a set of proposed metrics and key performance indicators was offered to enable the governing body to measure the conduct and effectiveness of the QRM program.

Chapter Ten finalized the Phase 3 research with a discussion around a QRM maturity measurement tool and assessment process developed by the researcher. The development of the measurement tool synthesized learnings from prior phases of the research into a simple approach to gauge the current level of QRM maturity of a site and define a path towards improvement. The QRM maturity measurement tool and assessment process was piloted at eight separate biopharmaceutical manufacturing sites, validated the tool as an appropriate means to measure QRM effectiveness.

Finally, Chapter Eleven outlined areas where additional research is warranted to more fully characterize and improve QRM in the pharmaceutical and biopharmaceutical industries.

According to Harvard Business Review Analytic Services, risk management programs cannot be successful without six organizational capabilities:

1. “Linking risk information to strategic decision making
2. Establishing a risk aware culture at all levels
3. Embedding risk management practices and responsibilities within strategy and operations
4. Ensuring that all decisions remain within the organization’s risk tolerance
5. Driving risk mitigation activities
6. Proactively identifying current and emerging risks” (164)

This thesis, and the research effort it described, sought to address each of these capabilities in turn, recoding QRM principles and practices to better manage risk to the patient.

In her learnings over the course of the research, the researcher has identified several recommendations for both regulators and industry to better support the common goal of applying QRM to manage risk to the patient. It is at this stage that the researcher chooses to exercise the advantages of her insider status, as summarized above and discussed at length in Chapter Three, and issue both parties an untitled letter. As the FDA as found untitled letter an effective means to incite action, so too hopes the researcher.

12.2 An untitled letter to regulators

Dear Sir or Madam:

Thank you for your service in protecting the public health. Patients the world over rely on you as the gatekeepers for the drug manufacturing industries, trusting they are safe under your watchful eyes. Your regulatory strategy is

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71 An untitled letter is a regulatory communication vehicle used by the US FDA to warn manufacturers of violative conditions that may, if left unresolved, trigger future regulation action.
evolving in ways that acknowledge emergent concepts, demonstrating your commitment to modernizing your way of thinking. Kudos to you and best of luck in this endeavor. I know it is difficult to change.

It has come to my attention that the use of quality risk management in the pharmaceutical and biopharmaceutical industries has not been successful in managing the risk to patients. This is alarming, particularly in light of your evolving regulatory strategy which relies on this very topic to supplement traditional regulation. If QRM fails to manage risk to patient, what good will it do? What will become of modern regulation if it so heavily relies on ineffective programs? What will happen to the patients?

There are actions that you, as regulators, can take to help make QRM successful and ensure its goal is met. Please consider the following as you continue along your mission:

- Several QRM experts have suggested that regulators may be confusing industry with regard to appropriate QRM application. (134) (132) (127) (125) One expert even went so far as to say that “regulators are part of the problem” with the immature state of QRM in industry. (134) For example, you often issue warning letters for cGMP violations, requiring a risk assessment to be performed in response. This implies to industry that it is your desire that QRM be performed retrospectively, perhaps, even, to justify the quality of a product already on market. Of course, this is the wrong impression. As a first step, please seek out better and more complete education on QRM principles and practices. This will enable you to ensure that your requests do not encourage improper practices within industry.
• Please review QRM in all inspections you perform. Industry has heard your message that QRM is an enabler of the quality system, and yet, many firms never get feedback on how their enabler is working. Please make a distinction between risk assessments and QRM in these inspections. Risk assessments are not representative of risk management. Training, governance, risk control, risk review, and risk communication must also be reviewed. After all, what can one make of a quality system that is not adequately enabled?

• Please be cautious of the language you select when issuing new regulation or guidance. For example, rather than requiring a risk assessment to be created for a given topic, consider requiring the risk to be assessed. This will allow industry to use their living risk assessment libraries to evaluate risks in the context of other risks to the patient, minimizing the number of individual, narrowly-scoped risk assessments that confound patient protection.

• Please take the time to review all regulations and guidance that you have issued to ensure they accurately reflect your intended message. Where discrepant points or inconsistencies are found, make industry aware of what you have learned and how you intended to resolve it. Risk communication can also flow from regulators to industry, you know.

• Please try to avoid suggesting a particular risk tool be used to assess certain types of risks. Frankly, you don’t have a great track record in getting this right (refer to sections 2.2.3 and 5.3.2), and it absolves industry from the responsibility to understand QRM well enough to select a tool on their own.

I know these recommendations and the concerns that inspire them may be hard to hear. They come from a good place—a place of devotion to well-done QRM
and a place of concern for the patient. Please, take these recommendations to heart. The patient depends on it.

Sincerely,
The Researcher

12.3 An untitled letter to industry

To Whom It May Concern (which, of course, means all of us):

I am sorry to inform you that QRM isn’t working. I don’t mean to say that QRM doesn’t work—indeed, it does—but rather the way we have tried to implement it has been unsuccessful.

I’m sure many of you have sensed this. We have been working so hard, doing the best QRM we know how to do. But it is like we are on an exercise wheel in a hamster cage—running, running, running, yet getting nowhere. We are creating a lot of risk assessments, a lot of deliverables, and yet our patients are no better protected. Things have got to change.

Please, stop doing what you’re doing. Review this thesis, dissolve your current QRM programs, and replace it with this one. I know some of us are doing good things with QRM, that there are pockets of best practices out there. I do not ask
those companies to take a step backward. What I ask is that we look critically at our QRM programs, that we gauge our maturity using the QRM maturity measurement tool provided in Appendix IV, and that, if we’re not where we need to be, we take a drastic leap forward.

This will require a lot from you. It will require some of us to stop managing and start leading. It will require us to invest in prevention, to invest in education, and to let some fires burn while we seek to prevent others. But ours is an industry of intelligent, resourceful, and resilient people. We are far more capable of managing quality risks than our patients.

Remember, people, processes, and governance need to work together to make QRM effective, and QRM is needed to support the patient. We can do this, and we shall.

Kind regards,
The Researcher
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112. **Hayhurst, Mark.** 'I knew what was about to happen'. *The Guardian.* January 22, 2001.


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135. **Interview with Siegfried Schmitt.** Principal Consultant, PAREXEL. January 26, 2016.


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## 14 Appendix I: Template for QRM Initiation

This appendix offers a template that may be used by pharmaceutical and biopharmaceutical firms to enhance their maturity in QRM Initiation. The use of this template will ensure that all aspects of the QRM Initiation process are performed in a concise and organized manner.

### Section 1: General Information

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### Section 2: Team Identification

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<tr>
<th>Expertise Needed</th>
<th>Subject Matter Expert Name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Manufacturing Process</td>
<td></td>
</tr>
<tr>
<td>[ ] Quality</td>
<td></td>
</tr>
<tr>
<td>[ ] Microbiology</td>
<td></td>
</tr>
<tr>
<td>[ ] Chemistry</td>
<td></td>
</tr>
<tr>
<td>[ ] Manufacturing Science</td>
<td></td>
</tr>
<tr>
<td>[ ] Validation</td>
<td></td>
</tr>
<tr>
<td>[ ] Engineering</td>
<td></td>
</tr>
<tr>
<td>[ ] Facilities</td>
<td></td>
</tr>
<tr>
<td>[ ] Maintenance</td>
<td></td>
</tr>
<tr>
<td>[ ] Calibration</td>
<td></td>
</tr>
<tr>
<td>[ ] Computerized Systems</td>
<td></td>
</tr>
<tr>
<td>[ ] Automation</td>
<td></td>
</tr>
<tr>
<td>[ ] Medical / Clinical</td>
<td></td>
</tr>
<tr>
<td>[ ] Toxicology</td>
<td></td>
</tr>
<tr>
<td>[ ] Other (specify)</td>
<td></td>
</tr>
</tbody>
</table>

System/Process Owner: ____________________________________________

Print / Sign                                                  Date
Section 3: Risk Assessment Decision Tree

Scope and Objective:

Risk Question

Is there a procedural requirement to use a specific risk tool? □ Yes □ No

Use tool defined in the applicable procedure

Is this a living risk assessment? □ Yes □ No

Risk Assessment Formality = Formal

Is the development of a sampling plan a primary objective? □ Yes □ No

Use Hazard Analysis and Critical Control Points (HACCP)

Is the objective of the risk assessment to determine patient impact following an event? □ Yes □ No

Risk Assessment Formality = Formal

Is the development of a sampling plan a primary objective? □ Yes □ No

Use Risk-based Impact Assessment (RBIA)

Is the objective of the risk assessment to determine root (or potential) cause? □ Yes □ No

Risk Assessment Formality = Formal

Is the issue simple and loosely coupled or complex and tightly coupled? □ Simple □ Complex

Use Failure Modes and Effects Analysis (FMEA) tool

Is this risk assessment related to a process or system that is critical to product quality or patient safety? □ Yes □ No

Risk Assessment Formality = Less Formal

Use Failure Modes and Effects Analysis (FMEA) tool

Use Risk Estimation Matrix (REM), Risk Ranking and Filtering (RRF), decision tree, Ishikawa diagram, or other risk-based approach
Level of Formality: □ Formal □ Less Formal □ Customized

Risk Tool: ________________________________________________

System/Process Owner: ____________________________________________

Print / Sign                                               Date

Section 4: Request Disposition

☐ Risk Assessment is approved to proceed based on the details of this template and site objectives as defined by the QRM Plan.

☐ Risk Assessment is NOT approved to proceed. Information in this template is incomplete or inaccurate, or request conflicts with the site objectives as defined by the QRM Plan.

Comments:

Approved by: ________________________________________________

Quality Risk Management; Print / Sign               Date
## Appendix II: Template for Risk Register

<table>
<thead>
<tr>
<th>Risk ID</th>
<th>Rev Info</th>
<th>Report #</th>
<th>Report Title</th>
<th>Revision</th>
<th>System/Process Owner</th>
<th>Approval Date</th>
<th>Failure Mode / Hazard</th>
<th>Failure Cause</th>
<th>Failure Effect</th>
<th>Likelihood</th>
<th>Detectability</th>
<th>Severity</th>
<th>Risk Level</th>
<th>Rationale for Acceptance</th>
<th>Mitigation Activity</th>
<th>Responsible Party</th>
<th>Target Implementation Date</th>
<th>Completion Date</th>
<th>Residual Risk</th>
<th>Acceptance Date</th>
</tr>
</thead>
</table>
## 16 Appendix III: Template for Quality Risk Profile

<table>
<thead>
<tr>
<th>Risk Identification</th>
<th>Risk Classification</th>
<th>Risk Analysis</th>
<th>Risk Control</th>
<th>Residual Risk</th>
<th>Risk Acceptance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk ID</td>
<td>Risk Description</td>
<td>Date</td>
<td>Risk Identified</td>
<td>Risk Type</td>
<td>Quality System Element</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


## 17 Appendix IV: Quality Risk Management Maturity Measurement Tool

<table>
<thead>
<tr>
<th>People</th>
<th>Maturity Level 1: Absent</th>
<th>Maturity Level 2: Novice</th>
<th>Maturity Level 3: Intermediate</th>
<th>Maturity Level 4: Expert</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organizational awareness</strong></td>
<td>There is no QRM training provided for most employees on site.</td>
<td>QRM training is provided at the site at an undefined frequency to those who request the training.</td>
<td>All employees are provided with training commensurate with their level interaction with risk management, including those with no direct responsibility for performing or participating in risk assessments (e.g. those who only require training on the role of QRM in GMP).</td>
<td>All employees are provided with training commensurate with their level interaction with risk management, including those with no direct responsibility for performing or participating in risk assessments (e.g. those who only require training on the role of QRM in GMP). Training is updated and refreshers are provided periodically; retraining frequency is predefined and documented.</td>
</tr>
<tr>
<td><strong>QRM expertise (facilitators)</strong></td>
<td>There is no training available to develop QRM experts.</td>
<td>QRM facilitator training focuses on the basic principles of QRM and the use of QRM tools.</td>
<td>QRM facilitator training includes QRM principles, QRM tools, best practices over the QRM lifecycle, and facilitation skills.</td>
<td>QRM facilitator training is considered an ongoing education. Facilitators undergo a rigorous qualification process consisting of the maturity level 3 coursework, and are required to apprentice under a seasoned QRM expert. QRM experts are expected to mentor apprentices and continue growing in their role.</td>
</tr>
<tr>
<td>Sub-heading</td>
<td>Maturity Level 1: Absent</td>
<td>Maturity Level 2: Novice</td>
<td>Maturity Level 3: Intermediate</td>
<td>Maturity Level 4: Expert</td>
</tr>
<tr>
<td>--------------------------------</td>
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<td>-----------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Application of QRM</td>
<td>Reactive only</td>
<td>Primarily reactive (80% reactive / 20% proactive)</td>
<td>Primarily proactive (80% proactive / 20% reactive)</td>
<td>QRM fully integrated throughout the quality system and is applied proactively to design systems and assess risks</td>
</tr>
<tr>
<td>Cultural motivation</td>
<td>achieve compliance; &quot;the regulations require it&quot;</td>
<td>foster more consistent decision-making</td>
<td>learning organization; continuous improvement of operations and business processes through risk</td>
<td>protecting the patient</td>
</tr>
<tr>
<td>Personnel engagement</td>
<td>individual heroics and silos</td>
<td>organization acknowledges QRM value proposition; pockets of personnel are engaged in QRM</td>
<td>organization is engaged in QRM; pockets of personnel advocate for QRM</td>
<td>organization advocates for QRM</td>
</tr>
<tr>
<td>Recognition and reward system</td>
<td>Heroic efforts for solving existing problems are rewarded exclusively; proactive QRM consciously deprioritized</td>
<td>Efforts for proactive QRM go unnoticed by the organization</td>
<td>Informal acknowledgement / rewards for proactive QRM, or rewards exist in pockets only</td>
<td>Formal recognition / reward system in place for proactive QRM</td>
</tr>
</tbody>
</table>
# QRM Initiation

<table>
<thead>
<tr>
<th>Sub-heading</th>
<th>Maturity Level 1: Absent</th>
<th>Maturity Level 2: Novice</th>
<th>Maturity Level 3: Intermediate</th>
<th>Maturity Level 4: Expert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk question</td>
<td>Individual risk assessments do not have clearly defined risk question or objective and scope.</td>
<td>Some risk assessments have a defined risk question and scope, however the risk question may imply a forgone conclusion.</td>
<td>Some risk assessments have a clearly defined risk question and scope, phrased in a way to encourage an assessment that is agnostic to the outcome.</td>
<td>All risk assessments have a clearly defined risk question and scope, phrased in a way to encourage an assessment that is agnostic to the outcome.</td>
</tr>
<tr>
<td>Tool selection</td>
<td>There are no QRM tools defined, or only a single QRM tool is in use.</td>
<td>A QRM toolkit is in place, but tool selection is inconsistent based on the risk question.</td>
<td>A QRM toolkit is in place. Guidance is available to ensure the tool selected is appropriate for the risk question.</td>
<td>A QRM toolkit is in place. There is a clearly defined mechanism to select an appropriate tool based on the risk question, with an allowance to use an alternate tool with appropriate rationale.</td>
</tr>
<tr>
<td>Expert representation</td>
<td>Teams of SMEs are not used to conduct a risk assessment.</td>
<td>Team selected for individual risk assessments do not adequately represent the technical expertise required.</td>
<td>Team selected for individual risk assessment represents the technical expertise required for the completion of a robust assessment.</td>
<td>Team selected for individual risk assessment represents the technical expertise required for the completion of a robust assessment, and the team members are empowered to make judgments representing their area of expertise. SME representation is consistent throughout the risk assessment.</td>
</tr>
<tr>
<td>Sub-heading</td>
<td>Maturity Level 1: Absent</td>
<td>Maturity Level 2: Novice</td>
<td>Maturity Level 3: Intermediate</td>
<td>Maturity Level 4: Expert</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Living risk assessment library</td>
<td>The living risk assessment library has not been defined.</td>
<td>The living risk assessment library has been defined. Between 0 - 50% of required risk assessments are complete.</td>
<td>The living risk assessment library has been defined. Between 51 - 80% of required risk assessments are complete.</td>
<td>The living risk assessment library has been defined. Over 80% of required risk assessments are complete and the remainder are planned.</td>
</tr>
<tr>
<td>Risk identification</td>
<td>Risks identified without any systematic mechanism. Clear gaps exist between site experience and identified risks. There is no link between the identified risks and elements critical to the patient (i.e. CQAs, CPPs, CAs, and CADEs).</td>
<td>Risks are systematically identified and aligned with site experience, however there is a weak link between the identified risks and elements critical to the patient.</td>
<td>Risks are systematically identified and aligned with site experience. Risk associated with most elements critical to the patient have been identified.</td>
<td>Potential risks are identified in a systematic way, consistent with the identified scope, perspective, and risk question. Identified risks are comprehensive with respect to reasonable expectations when compared with site experience. Risks associated with all elements critical to the patient have been identified.</td>
</tr>
<tr>
<td>Risk analysis</td>
<td>Individual risk assessments are based on undocumented or invalid assumptions and are largely subjective with no references to supporting data.</td>
<td>Individual risk assessments have some undocumented assumptions. Supporting data is referenced but there is no discussion of the how the data relates to the analysis.</td>
<td>Individual risk assessments include a general discussion of assumptions. Supporting data is referenced and discussed in the context of the analysis.</td>
<td>Individual risk assessments performed using clearly referenced data sources, with documented rationale connecting the related data to each risk that was analyzed. All assumptions are valid and documented.</td>
</tr>
<tr>
<td>Risk evaluation</td>
<td>The risk evaluation is not connected to the risk analysis. Claims of risk acceptability are made without consideration of risk tolerance.</td>
<td>The risk evaluation is derived from the results of the risk analysis but does not adequately align with the associated risk tolerance.</td>
<td>The risk evaluation is derived from the results of the risk analysis and is aligned with the applicable risk tolerance.</td>
<td>Risk evaluation is derived from the results of the risk analysis and is aligned with the applicable risk tolerance. Individual risks are evaluated and accepted on a case-by-case basis rather than through a comparison with a risk threshold.</td>
</tr>
<tr>
<td>Risk Control</td>
<td>Sub-heading</td>
<td>Maturity Level 1: Absent</td>
<td>Maturity Level 2: Novice</td>
<td>Maturity Level 3: Intermediate</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
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<td>--------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Risk control option analysis</td>
<td>Risks deemed unacceptable through risk evaluation do not continue to risk control.</td>
<td>All unacceptable risks continue to risk control, however there is no consistent or documented rationale for the selection of mitigation activities.</td>
<td>All unacceptable risks continue to risk control, and the selection of mitigation activities is appropriate and includes a documented rationale.</td>
<td>All unacceptable risks continue to risk control. Evidence that the mitigation strategy selected is optimal based on the anticipated effectiveness of the risk control, the individual risk or group of risks that are targeted for reduction, the root cause of those risks, anticipated residual risk, and new risks that may arise as a result of each. Rationale for selection of mitigation strategy is documented.</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>Documented risk mitigation activities are not consistently implemented.</td>
<td>Documented risk mitigation activities are implemented as defined, and presumed to be effective in reducing the risk.</td>
<td>Documented risk mitigation activities are implemented as defined, and evaluated for effectiveness in reducing the risk.</td>
<td>Documented risk mitigation activities are implemented as defined, and evaluated for effectiveness in reducing the risk. There is an analysis and appropriate action taken in the event new risks are introduced (or existing risks affected) through the implementation of the mitigation activities.</td>
</tr>
<tr>
<td>Residual risk appraisal</td>
<td>Residual risk is not evaluated following mitigation.</td>
<td>Appraisal (acceptance or rejection) of residual risk is documented with no rationale.</td>
<td>Appraisal of residual risk, including rationale, is documented in every assessment.</td>
<td>Comprehensive, documented rationale included to describe the acceptability of both individual and overall residual risk.</td>
</tr>
</tbody>
</table>
### Risk Review

<table>
<thead>
<tr>
<th>Sub-heading</th>
<th>Maturity Level 1: Absent</th>
<th>Maturity Level 2: Novice</th>
<th>Maturity Level 3: Intermediate</th>
<th>Maturity Level 4: Expert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk review structure</td>
<td>There is no defined process for risk review.</td>
<td>There is a defined process for risk review, but data sources and expectations for analysis and conclusions are weakly defined.</td>
<td>There is a defined process for risk review. Internal data sources and expectations for analysis and conclusions are clearly defined.</td>
<td>There is a defined process for risk review, including both periodic and event-driven reviews. Internal and external data sources are defined, and expectations for analysis and conclusions are clear.</td>
</tr>
<tr>
<td>Risk review execution</td>
<td>Risk review has not been performed.</td>
<td>There is limited evidence of data being analyzed during risk review.</td>
<td>There is evidence of internal data sources (e.g. deviations, change control, related ad hoc risk assessments) analyzed during risk review. The rationale behind conclusions drawn is documented and is aligned with the data reviewed.</td>
<td>There is evidence of both internal (e.g. deviations, change control, related ad hoc risk assessments) and external data sources (e.g. regulatory intelligence, industry benchmarking, etc.) analyzed during risk review. The rationale behind conclusions drawn is documented and is robust, identifying specific connections between sources of information and related updates to the living risk assessment.</td>
</tr>
</tbody>
</table>
## Risk Communication

<table>
<thead>
<tr>
<th>Sub-heading</th>
<th>Maturity Level 1: Absent</th>
<th>Maturity Level 2: Novice</th>
<th>Maturity Level 3: Intermediate</th>
<th>Maturity Level 4: Expert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk communication plan</td>
<td>No formal or defined requirements associated with communication relative to the person performing the communication, the parties receiving the communication, or the content, format, intent, or frequency of communication.</td>
<td>Mechanism for communication is defined, however is uniform with respect to the form and audience of communication vs. what is being communicated.</td>
<td>Several different mechanisms for communication are defined. Mechanism outlines communication pathways throughout the organization as well as with external stakeholders.</td>
<td>A formalized risk communication plan exists, which defines several communication pathways based on nature of the communication, the intent of the communication, the format of communication, and the communicator and recipient.</td>
</tr>
<tr>
<td>Communication of risks</td>
<td>Risks are not communicated.</td>
<td>Risk communication is infrequent, passive, unclear, or sporadic.</td>
<td>Risk communication is performed frequently between necessary parties.</td>
<td>Continuous risk communication occurs. Format of communication is tailored to what is being communicated (e.g. email, phone call, meeting discussion, formal documentation). Communication is clear in terms of what the expected result will be (e.g. to inform or to initiate action). All communication forms a closed loop so there is no ambiguity regarding whether the message has been understood.</td>
</tr>
</tbody>
</table>
# QRM Infrastructure

<table>
<thead>
<tr>
<th>Sub-heading</th>
<th>Maturity Level 1: Absent</th>
<th>Maturity Level 2: Novice</th>
<th>Maturity Level 3: Intermediate</th>
<th>Maturity Level 4: Expert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roles and responsibilities</td>
<td>Roles and responsibilities within the QRM program are not defined.</td>
<td>Roles and responsibilities are defined, but are isolated to a single functional group.</td>
<td>Roles and responsibilities are defined, including the Head of QRM, System and Process Owners, Subject Matter Experts, Quality Unit, and senior management.</td>
<td>Roles and responsibilities are defined, including the Head of QRM, System and Process Owners, Subject Matter Experts, Quality Unit, and senior management. All personnel fulfill their responsibilities under the QRM program.</td>
</tr>
<tr>
<td>Dedicated QRM staff</td>
<td>There are no staff responsible for the QRM program.</td>
<td>One or more staff is responsible for the QRM program as a portion of their job description.</td>
<td>There is a defined Head of QRM.</td>
<td>There is a functional group dedicated to the QRM program, of an appropriate number based on site need. The Head of QRM has direct access to senior management through his or her reporting structure.</td>
</tr>
<tr>
<td>Qualified facilitators</td>
<td>There are no qualified facilitators on site.</td>
<td>Site has a defined group of qualified facilitators, however either:</td>
<td>Site has an optimal number of qualified facilitators that is sufficient to meet site needs and ensure the facilitator's knowledge and experience remains current. Several of the facilitators are experts in QRM and can be relied upon to improve the effectiveness of the QRM program.</td>
<td>Site has an optimal number of qualified facilitators that is sufficient to meet site needs and ensure the facilitator's knowledge and experience remains current. Several of the facilitators are experts in QRM and can be relied upon to improve the effectiveness of the QRM program.</td>
</tr>
<tr>
<td>Sub-heading</td>
<td>Maturity Level 1: Absent</td>
<td>Maturity Level 2: Novice</td>
<td>Maturity Level 3: Intermediate</td>
<td>Maturity Level 4: Expert</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
<td>-------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Risk Register</td>
<td>There is no risk register for the site.</td>
<td>There is a risk register at the site that is updated sporadically or contains minimal information.</td>
<td>There is a risk register in place that is updated consistently. The register contains adequate information to enable the tracking of the site's most critical risks.</td>
<td>There is a risk register in place that is updated consistently. The register contains adequate information to enable the tracking of the site's most critical risks. The risk register is reviewed at the appropriate governance forum. There is a defined escalation pathway to ensure the register is visible to senior management.</td>
</tr>
<tr>
<td>Quality risk profile</td>
<td>There is no quality risk profile for the site.</td>
<td>There is a quality risk profile at the site that is updated sporadically or fails to capture key strategic quality risks.</td>
<td>There is a quality risk profile in place that is updated consistently. All strategic quality risks are captured and addressed as appropriate. The quality risk profile is created by the appropriate governing body.</td>
<td>There is a quality risk profile in place that is updated consistently. All strategic quality risks are captured and addressed as appropriate. The quality risk profile is created by the appropriate governing body. Decisions regarding strategic site objective, such as project planning and budgeting, are made in consideration of the quality risk profile.</td>
</tr>
<tr>
<td>QRM Plan</td>
<td>The site does not have a defined QRM plan.</td>
<td>The site has a QRM Plan that focuses primarily at the activity level.</td>
<td>The site has a QRM Plan that fully maps strategy to individual QRM activities over a defined timeframe.</td>
<td>The site has a QRM Plan that fully maps strategy to individual QRM activities over a defined timeframe. All personnel have visibility to the QRM Plan and the way in which their work influences the achievement of objectives is both clear and well understood.</td>
</tr>
<tr>
<td>Metrics and KPIs</td>
<td>The site has not defined metrics for the QRM program.</td>
<td>QRM metrics focus on compliance and lagging indicators rather than effectiveness and leading indicators.</td>
<td>QRM metrics include a mix of compliance and effectiveness measurements as well as lagging and leading indicators.</td>
<td>The site has defined metrics and KPIs representative of all stages of QRM, compliance and effectiveness, and lagging and leading indicators. Metrics and KPIs are tracked on a defined frequency and reviewed by applicable governing body. KPIs indicate that QRM effectiveness is stable or improving.</td>
</tr>
</tbody>
</table>


Guest editor of special double issue of *Journal of Validation Technology*, dedicated to Quality Risk Management. December 2015.


