

Patient Safety in Quality Management Operations: Assessing the maturity of Quality Risk Management (QRM) strategies within a Start-up CDMO

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## **Abstract**

This applied doctoral project examined the maturity of Quality Risk Management (QRM) strategies within a start-up Contract Development and Manufacturing Organization (CDMO), referred to as Startup X. The study addressed the critical problem of underdeveloped QRM systems in early-stage CDMOs, where limited resources, leadership instability, fragmented governance, and reactive quality risk cultures compromise manufacturing reliability, product quality, regulatory compliance, and ultimately – patient safety. These gaps impede internal operational efficiency, organizational performance, and pose broader public health risks by increasing the risk of quality failures, production delays, and drug shortages across the biopharmaceutical supply chain.

The project aimed to evaluate the current maturity of Startup X's QRM framework, identify systemic and cultural barriers, and develop evidence-based strategies to strengthen quality governance and patient-centered decision-making. Guided by Waldron's (2017) QRM Maturity Model, this qualitative case study employed semi-structured interviews, document reviews, and process mapping to assess QRM practices. Participants included Quality Control personnel and senior leaders with direct involvement in quality operations. Data was thematically analyzed to identify recurring patterns related to risk management practices, communication, and governance structures.

The findings indicate that Startup X is in the emergent to early developing stages of QRM maturity. Key challenges included limited staff competency, inconsistent application of risk assessment tools, insufficient training, and weak cross-functional governance. Despite these limitations, the project successfully established a diagnostic baseline for QRM capability and produced a structured roadmap for improvement. Immediate objectives emphasize embedding

risk-based decision-making through a formal QRM charter, assigning risk ownership roles, and instituting comprehensive training programs to cultivate a proactive quality culture.

The conclusions of this project provide practical strategies for Startup X and similar CDMOs to progress toward structured and sustainable QRM maturity. Strengthening governance frameworks, standardizing QRM practices, and institutionalizing proactive risk management will enhance regulatory compliance, client confidence, and patient protection, thereby advancing professional practice and quality excellence within biopharmaceutical manufacturing.

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## **Section 1: Foundation**

Drug recalls, shortages, and supply disruptions frequently arise due to manufacturing quality issues, which may include subpotency, lack of sterility, and product mix-ups. Common challenges include contamination and failure to comply with Good Manufacturing Practices (GMP). As such, it is crucial to effectively address these issues to ensure the reliability of drug products and to mitigate any potential threats to healthcare delivery and, ultimately, patient safety. To begin with, due to their significant impact on human health, drug products must meet stringent quality standards. The absence of essential medications, such as chemotherapy agents, analgesics, and antibiotics, poses serious risks for patients in need of treatment. Shortages of essential medications pose significant health risks, particularly for cancer patients. These shortages can delay treatment and force physicians to consider sub-optimal alternatives. Additionally, Quality issues, such as packaging errors, may lead to adverse effects. While the FDA addresses manufacturing deficiencies, manufacturers ultimately bear the responsibility for maintaining quality (Cundell, 2020). Drug shortages have become more common, with medications on shortage lists increasing from 61 to 178 between 2005 and 2010, and over 200 reported in 2012 (Caulder, 2015). Resolving Drug shortage problems requires establishments to devote time and resources to implement remedial actions.

Addressing drug shortages requires organizations to invest time and resources in effective solutions. For developers of Cell and Gene Therapies (CGT), a major challenge is effectively translating biological concepts into scalable and manufacturable treatments—an essential step for achieving commercial success. As a result, many companies are increasingly collaborating with Start-Up Contract Development and Manufacturing Organizations (CDMOs). These CDMOs offer vital solutions in drug product manufacturing, enabling companies to manage capital

expenditures while identifying necessary process modifications for development and optimization. CDMOs offer a diverse range of solutions throughout the drug manufacturing process. They are essential in pinpointing key process modifications that can deliver substantial value. Additionally, CDMOs advocate for a systematic approach to drug development, manufacturing, and optimization, which improves overall efficiency and effectiveness. As highlighted by Cook (2022), Drug product recalls can lead to substantial financial losses and may require facility shutdowns for remediation, causing significant disruptions in production. Consequently, it is crucial for emerging CDMOs to address challenges that could lead to suboptimal products, including risks associated with existing manufacturing processes and changes that do not align with target scales.

Start-up CDMOs must work to gain proficiency in CGT clinical batch manufacturing, becoming more relevant in CGT clinical development and providing flexibility in the face of high changeover and portfolio shifts. Price is a priority topic when a client decides to work with a CDMO – however, patient-centered clinical development also requires careful assessment and budgeting. Building a scalable CDMO in the CGT industry requires continuous evaluation of structure, resources, and technologies. The key to a Start-Up CDMO's success is having the technical expertise to meet tight deadlines and customize manufacturing processes to meet individual client needs while ensuring compliance with regulatory and quality standards. Being a client-centric CDMO is critical to ensuring every project – large or small – receives focused attention and specialized handling. It's an approach that transforms potential challenges into successful outcomes. However, since the outcome involves patients and their needs, then it is imperative to ensure processes are monitored in real-time with process inefficiencies either reduced or eliminated.

This dissertation proposal aims to focus on the elements that a robust QRM system canopy at a Start-Up biopharmaceutical company – particularly assessing CDMO QRM maturity, accessibility, and reliability. Biopharmaceutical companies without well-established Quality Risk Management (QRM) processes may struggle to effectively integrate quality clinical operations data, hindering their ability to conduct thorough analyses and gain valuable insights into their operations and potential quality-related risks. Moreover, they may be hesitant to embrace changes, whether technological, procedural, or conceptual, that could enhance their operations. This limitation can impede their capacity to identify opportunities for improving production and business processes. In contrast, Biopharmaceutical companies that have a more mature QRM process in place can leverage relevant data and knowledge, allowing them to optimize both production and business operations. As such, Waldron's (2017) qualitative research sought to delineate the stage of QRM implementation maturity comprehensively, presenting a spectrum from low to high maturity levels, and consequently developed an assessment model for QRM maturity with suitable tools for improvement in manufacturing processes necessary to safeguard patients from the risks associated with low-quality medicinal products. Waldron's (2017) review examines the ability of biopharmaceutical organizations to synthesize information from various sources, propose suitable solutions, and ensure their successful implementation to improve business operations and production processes. Moreover, Waldron's (2017) research study evaluated 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.

The implementation of QRM quality control measures can precipitate supply chain challenges, such as delays in the distribution of drug products to healthcare providers and

patients. Moreover, pharmaceutical companies facing product recalls and subsequent protracted supply disruptions may also encounter substantial reputational damage. As such, this dissertation proposal concerns the need for CDMOs to improve in the use of risk-based principles and tools to ensure that the manufacturing processes used to produce medicines, and their related equipment are appropriate. CDMOs should be able to identify the biggest value-add process modifications and recommend a QRM approach that is critical for drug product optimization. Manufacturing processes need to be validated (or proven) to demonstrate that they can produce a medicine of the required quality. The items of equipment used in such processes need to be qualified to prove that they are fit for their intended use.

QRM Maturity is crucial for achieving high-quality standards in CGT. The implementation of QRM maturity tools within CDMOs can significantly enhance their qualification and validation processes. However, the current state of QRM practices in most CDMOs remains largely uncharted. This creates a considerable gap in understanding the factors that drive the development of more sophisticated and effective risk management strategies in the unique context of CDMOs. By evaluating these factors, CDMOs can better navigate the complexities of quality assurance in CGT. Key areas to explore include organizational culture, regulatory frameworks, quality systems and operations, technological advancements, and the specific dynamics of the CGT market. An in-depth examination of these components will provide CDMOs (particularly Start-Up CDMOs with immature QRM tools), with valuable insights, enabling them to navigate the intricacies of quality assurance in CGT effectively. This knowledge is essential not only for enhancing operational efficiency but also for fostering a

robust quality ecosystem that ultimately leads to improved patient outcomes in the rapidly evolving field of CGT.

### **Statement of Problem**

The management problem is to improve the maturity and robustness of quality risk management (QRM) strategies in the manufacturing process of cell and gene therapies for a startup CDMO. The problem to be addressed in this dissertation project is that the maturity of current QRM strategies being used by Startup X is unknown. Understanding the current level of QRM quality is an important foundation in the development of high quality, mature QRMs that promote both high quality production and manufacturing processes and patient safety practices.

In-mature (or minimal) QRM strategies can contribute to drug product recalls, drug shortages, and treatment delays. Drug product shortages pose a significant threat to public health and healthcare delivery by undermining the ability to provide timely and high-quality care to patients. This was evident during the COVID-19 pandemic in 2020. According to Dharmasena (2024), the pandemic caused the pharmaceutical industry and healthcare providers such as hospitals and pharmacies, to experience significant disruptions. This comprised facility shutdowns, unprecedented supply chain challenges, and quality system limitations (e.g., physical signatures, drug product labeling, investigations, document originals, risk assessments, and audits). Additionally, Johnston (2022) states that medical product shortages can affect patients in myriad ways, from poor clinical outcomes to other detrimental experiences that affect their quality of life. A 2019 global scoping review synthesized literature on the economic, clinical, and humanistic effects of drug shortages on patient outcomes in the United States and other countries (Phuong et al., 2019), found that during times of shortages, clinical outcomes

associated with the effects of shortages included increases in drug errors, adverse events, and mortality.

### **Purpose Statement**

The purpose of this applied qualitative case study is to evaluate the maturity of QRM strategies used by a CDMO start up. Understanding the current rigor and robustness of QRM strategies provides allows for the development of higher quality QRMs and the identification of factors that influence the consistency of implementing mature QRM measures for all clients and CGT manufacturing processes. A comprehensive evaluation of QRM implementation strategies and tools allows for improved quality control along the pharmaceutical manufacturing supply an distribution chain (Bhagat & Kanyal 2024). With pharmaceutical supply chains extending back to manufacturers all around the world, this assessment aims to gauge the impact of implementing robust QRM quality control measures throughout the manufacturing process, which is needed to protect patients from the risks associated with low-quality medicinal products. This can be achieved by conducting thorough product testing and analysis, adhering to Good Manufacturing Practices (GMP) standards, and investing in advanced manufacturing technologies for process optimization and automation. In the pharmaceutical and life sciences industry, maintaining high-quality standards is essential for safeguarding patient safety, ensuring regulatory compliance, and fostering trust and confidence in healthcare products and services. MacGillivray (2020). These techniques involve performance assessment and the use of findings to steer change in current quality standards.

The purpose statement indicates strategy assessments for uncovering the root causes of this seemingly intractable issue. The FDA continues to respond to poor manufacturing practices via compliance and enforcement actions, but the responsibility for the application of quality

management techniques in manufacturing processes would imply that reliable, high-quality manufacturing is attainable. However, in an area where the stakes are so high, why is this not being achieved? According to Cameron (2021), in the mid-late 1990s, the U.S. experienced a striking cluster of manufacturing failures and related enforcement actions, including government legal interventions such as injunctions and consent decrees. Subsequently, in the early 2000s, the FDA evaluated the situation. It was obvious that, despite significant FDA inspection and compliance activities, the quality of pharmaceutical manufacturing was uneven, and substandard practices were not uncommon.

As part of its role as a regulatory body in charge of supervising the quality of drug products and medications coming out of manufacturing facilities, the FDA enforces regular assessments of Current Good Manufacturing Practices (GMP). Aside from the United States, regulatory guidance has been put in place by organizations such as the World Health Organization, providing member states with basic standards to develop similar standards within their own regulatory frameworks. Through collaboration, innovation, and a commitment to quality excellence, the healthcare industry can continue to deliver safe, effective, and innovative healthcare solutions to patients worldwide.

### **Nature of the Project**

This section presents an overview of the methods used for this project. A more detailed discussion of the project's method and design can be found in Section 2. The strategy outlined in this project is focused on addressing shortages stemming from manufacturing and quality issues during batch release. Following manufacturing and release, the subsequent step in the supply chain is often referred to as the handover to the first economic customer. Therefore, it is essential to maintain an effective QRM (Quality Risk Management) system that provides a robust

framework for ensuring efficient, proactive, risk-based, and data-driven decision-making.

Shenoy (2021). QRM should foster innovation by expediting the implementation of changes that minimize the risk of quality failures and manufacturing issues, while enhancing process capability. QRM is an integral part of GMP compliance, enabling manufacturers to identify and mitigate risks throughout the product lifecycle, from raw material sourcing to distribution. As such, it is imperative to measure QRM maturity as part of the GMP approach.

Waldron's (2017) dissertation research comprehensively performed a QRM maturity assessment. The QRM maturity measurement tool is utilized to conduct a comprehensive assessment of the QRM program on site. This encompasses an evaluation of the program's design, as evidenced by policies and procedures, as well as the implementation of the program, as evidenced by completed QRM documentation and interviews with site personnel. The average value 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. The QRM maturity assessment which will be delved further into section 2, is conducted using an evidence-based approach. This involves reviewing randomly-selected samples of QRM documentation and interviewing individual QRM practitioners to determine the best-fit maturity score for each sub-heading in the measurement tool. Since it's not practical or valuable to review every single piece of evidence related to the QRM program, the random sampling is assumed to be representative of the entire population, allowing for the characterization of QRM practices as a whole.

The QRM maturity assessment studied in Waldron (2017) research was intended to be performed for a single site within a given pharmaceutical or biopharmaceutical company, which directly correlates to the scope of this dissertation project, as only one CDMO Manufacturing start up site is being studied. This is beneficial to the dissertation project as 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. Furthermore, it is imperative that 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. The CDMO Manufacturing site may choose to incorporate the maturity assessment into the self-inspection program as an additional way to evaluate the effectiveness of their quality system using Quality Risk Management (QRM). According to Waldron (2017), the assessor reviews the evidence and then selects the most appropriate maturity score for each sub-heading based on the defined criteria in the measurement tool. After scoring all sub-headings, the results are averaged for each heading, resulting in a total of eight individual scores: People, QRM Initiation, Risk Assessment, Risk Control, Risk Review, Risk Communication, QRM Infrastructure, and Governance. These scores are then displayed on a QRM maturity dashboard for further analysis. In this dissertation paper, QRM maturity aims to provide insight into whether QRM has enhanced industry compliance with cGMP and whether QRM itself is being applied in a compliant manner at the Start up CDMO Manufacturing site. As such, exploring QRM maturity assessment tools through a rigorous academic evidence-based framework further enhances knowledge of pharmaceutical quality and ultimately enables better service to the patient.

### **Needs Assessment**

When drugs become unexpectedly unavailable in the manufacturing supply chain, risk-based decision-making enables companies to provide key risk-indicating information to stakeholders and health authorities in a timely manner before the shortage becomes severe.

Incorporating QRM principles, knowledge management, and a comprehensive understanding of patient impact during shortages presents companies with the opportunity to uphold quality control systems effectively through informed and prompt decision-making. As such, timely and proactive measures amongst key stakeholders and health authorities should:

- Ensure strong management accountability
- Foster a sustainable quality culture that enables employees to speak up
- Reward behaviors that drive joint ownership between operations and quality units for timely issue resolution
- Build people skills and capabilities that drive change leadership and excellence in pharmaceutical operations
- Establish a governance model that tracks operational and quality performance with appropriate metrics.

Moreover, as part of a robust quality system, companies should implement QRM principles and knowledge management capabilities to accomplish the following:

- Proactively identify what controls are, and are not, in place for shortage prevention (for critical products at least)
- Proactively identify and control risks of interruption in manufacturing and product supply
- Link to clinical and safety risk assessments for their products
- Facilitate risk-based decision-making by companies and health authorities in response to shortages in order to control and reduce harm to patients

## **Project Questions/ Objectives or Goals**

**PQ1.** What is the current level of maturity of Startup X's quality risk management strategies?

**PQ2.** What evidence-based improvements can be recommended to improve the maturity of Startup X's current QRM program?

**PQ3.** What are the primary barriers encountered by Startup X in improving the maturity of risk management strategies?

## **Introduction to the Professional and Conceptual Framework**

This applied dissertation project will use the Quality Risk Management (QRM) framework to address the project questions. This section provides a brief overview of the framework. A more detailed discussion can be found in the literature review section below. Having a thorough understanding of the entire manufacturing process and supply chain, including the transfer of products to the first economic customer (healthcare providers), is crucial for effective management of potential drug shortages. Once hazards are identified and risks assessed, appropriate measures can be implemented to control, mitigate, or eliminate these risks. However, it's important to note that not all hazards can be anticipated, so regular review and assessment of new information is essential to ensure timely implementation of risk control actions.

The conceptual framework showcases the availability of knowledge regarding process-performance and product-quality monitoring systems that can enhance process understanding. An effective QRM system can distinguish between changes that necessitate regulatory reporting and those that can be managed independently. Yu L. X. (2018). Successful QRM empowers a company to showcase its grasp of the existing production process, including associated risks,

impacts, and risk mitigation strategies within the process. This comprises a holistic, risk-based framework:

- At a product level for the prevention and management of drug shortages caused by manufacturing and quality issues. Here, an end-to-end understanding of the value chain for manufacturing and distribution provides the ability to understand and implement end-to-end controls.
- At the system level, appropriate oversight and a robust pharmaceutical quality system (PQS) ensure compliance with applicable laws and regulations.

Both approaches should also establish mechanisms that provide early warning signals of potential shortages, including near-misses, assess potential root causes for the shortage considering multiple aspects, drive targeted manufacturing and product quality improvements (e.g., introduction of new technologies, continual improvement, innovation), and enable timely communications with key stakeholders and health authorities. Itri et al (2017).

Moreover, further aspects for proactive prevention of drug shortages include:

- A risk triage model that can be used to assess drug shortage risks and implement appropriate controls in the end-to-end value chain for the manufacturing and distribution of a product
- Response Plan at a product level.

In addition to internal risk and knowledge management, it is beneficial to implement systems that provide reliable and current information about the healthcare industry for a company's products, including demand trends, usage volumes, and market-share data. This collective body of information is valuable for decision-making by both the manufacturing company and health authorities in addressing shortages. Alanazi (2023). It enables both parties to comprehend the

risks of a shortage to patients, communicate advice to healthcare providers, and promptly take necessary measures to address a drug shortage. It is essential to have access to information about competitor products and alternative therapies in order to assess the risks of potential shortages. However, this information may not always be readily available due to confidentiality and other factors. For example, in the event of a shortage, having this information can help increase the supply of an alternative product, if available, in order to minimize the impact on patients. Mosadeghrad AM (2023).

In addition, the ICH calls for process and product monitoring throughout product development and commercial manufacturing, so the information can be used to establish and actively manage a timely control strategy for manufacturing. Moreover, management review of process performance and product quality should identify appropriate actions for continual improvement, such as the capture and dissemination of knowledge and the identification of post-approval changes (PAC).

Most companies have mechanisms to respond to drug shortages when they occur; however, these mechanisms might not be comprehensive or fully integrated into company procedures. A comprehensive approach for managing potential drug shortages should involve:

- Ability to respond quickly to minimize the impact of a shortage
- Framework for anticipating drug shortage triggers and risks and for establishing mechanisms to control risks and prevent shortages
- Mechanisms and processes for timely communications

As such, Good Practice Guide: Reducing Risk for Drug Product Shortages by EPIPA, describes a "good practice" model that a company can adopt to prevent and/or manage potential drug shortage situations. A company's QRM policy and related procedures should address risks

to patient safety in the context of product quality and availability. Typically, risk ranking levels in a company's QRM policy include ranking for GMP and regulatory compliance risks and patient safety risks based on product quality. Phuong (2019), provides an example of a risk ranking scale that incorporates considerations for both product quality and product availability in the ranking of patient safety risks.

While manufacturing and quality issues could impact product quality or patient safety, there may be instances when product quality or patient safety are not impacted. Still, there may be issues with regard to compliance with GMP or GDP or regulatory commitments provided in the product dossier. When handling GMP and regulatory compliance issues or deviations that may negatively impact the release of a product, the company must quickly identify the potential issue and work on a solution to mitigate the risk of a drug shortage. Hence, it is important that the education and qualification of employees who manage deviations include aspects associated with the assessment of potential supply impact in case an issue evolves further.

It is also important to establish mechanisms for escalating these GMP, GDP, and regulatory compliance issues to the appropriate level of management, as solutions might often require the allocation of resources and identification of alternatives. Companies often handle such issues internally, but they should involve the relevant health authorities early on in case there is a potential risk of a drug shortage, and a solution is unachievable in a short timeframe.

## **Definitions of Key Terms**

### **CDMO**

CDMO stands for Contract Development and Manufacturing Organization, which is a third-party company that provides services to pharmaceutical companies throughout the drug development and manufacturing process.

## **CGT**

Cell and gene therapy (CGT) is the use of genetic material inside the patient in the treatment or prevention of a disease. This can be done by adding or deleting, regulating, repairing or replacing a genetic sequence, and employed for both inherited and acquired diseases. When cells become damaged or start to malfunction, this can lead to diseases. Cell therapy is achieving the prevention or the treatment of such diseases through the transfer of living cells to a patient. CGT is one of the fastest growing fields in modern healthcare. By targeting diseases at the genetic and cellular level, CGTs offer an unprecedented opportunity to provide groundbreaking treatments that could prevent, halt or even reverse individual conditions.

## **GMP**

GMP stands for Good Manufacturing Practices, which is a set of quality assurance standards that ensure products are consistently produced and meet the required quality standards. GMP processes consist of the requirement to validate critical steps in the manufacturing process and key changes to the process. Validation is the documented act of demonstrating that instruments, processes, and activities function according to expectations. GMP processes ensure that medicines are produced to the quality standards outlined in the product specification, clinical trial authorization, or marketing authorization. GMPs also cover legal responsibilities, such as how to respond to complaints and product defects.

## **ICH**

The International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use is an initiative that brings together regulatory authorities and the pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product development and registration. ICH's mission is to achieve greater harmonization worldwide to

ensure that safe, effective and high-quality medicines are developed, registered and maintained in the most resource-efficient manner whilst meeting high standards.

**Quality Risk Management:** A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle

### **Response Plan**

A document that provides a structured action plan to proactively prevent drug shortages and also respond to a shortage in the event that one occurs. This also may also be known as a "Drug Shortage Prevention and Mitigation Plan."

**Risk Assessment:** Researchers like [Hewitt, P. et al. (2024)] and [Wang, X. et al.] discuss the use of risk scoring matrices based on severity, occurrence, and detectability to prioritize risks and allocate resources effectively.

### **Risk-based Triage for Drug Shortages**

A process of assessing and assigning priorities for managing drug shortage risks based on criticality and impact.

**Risk Communication and Monitoring:** The need for transparent communication of identified risks to relevant stakeholders and continuous monitoring of risk profiles is emphasized by Noordhuizen & Cannas (2009) and Ghezavati et al. (2013).

**Risk Identification:** Studies by [Mizrak, K. C. (2024)] and [Sezen, B. (2021)] emphasize the importance of comprehensive risk identification processes, including FMEA (Failure Mode and Effects Analysis) and brainstorming techniques, to capture potential quality risks across all stages of product development and manufacturing.

**Risk Mitigation:** Literature from [Samardelis and Cappucci, 2009] and [Agoston et al., 2011] explores various risk mitigation strategies such as design changes, process improvements, enhanced monitoring, and contingency planning.

### **Risk Priority Level**

A relative priority ranking assigned to a risk based on a combination of (a) therapeutic use of a product and patient impact due to product unavailability, (b) availability of alternatives, and (c) likelihood of a shortage.

### **Root-Cause Analysis**

A method employed to recognize patterns and evaluate potential risk in scenarios where human error is suspected. This method operates on the premise that systems, rather than individual elements, typically serve as the primary source of issues. Talebpour (2023).

### **Literature Review**

The following section presents a detailed discussion of the literature that exposes the deficiencies in the current Quality Management practices regarding the implementation of proactive approaches in preventing quality failures. Despite the wide appeal to adopt ‘Risk-based methodologies’ in quality management, many contemporary quality management studies have ignored it. Thus, in seeking to overcome these deficiencies/gaps, this study has developed an innovative Project Quality Risk Management (PQRM) model including QRM. The literature review concludes with an examination of the strengths and weaknesses of the evidence as it relates to this applied dissertation project. This section includes a discussion of the conceptual framework that will be used to guide the case study design to include: 1) an introduction of implementation science; 2) characteristics of complex interventions; 3) and the Consolidated Framework for Implementation Research (CFIR).

This proposed research aims to investigate the impact of implementation of a new risk assessment tool, integration of data analytics in risk identification, and leadership training on QRM effectiveness on quality outcomes within pharmaceutical manufacturing at Start Up CDMOs by examining the correlation between risk mitigation strategies and product quality, the influence of organizational culture on risk reporting behavior, as well as QRM Maturity.

This literature review is structured to assess QRM concepts. Although it is relatively new, there is a need to put in more effort to explore deeper to understand the related/underlying concepts and the associations among them. Some studies on Quality Risk Management have been done in relation to the Healthcare (ICH Q9) and pharmaceutical industry, of which ICH9 has been taken seriously to the extent of getting recognition as part of regulatory requirements. ICH Q9 - Quality Risk Management provides an excellent high-level framework for the use of risk management in pharmaceutical product development and manufacturing quality decision-making applications. Frank et al. (2009) prepared a database of case studies representing a range of quality-specific applications and risk management tools in a structured format, which demonstrate that there is a wide range of applications for the use of structured risk management analysis to facilitate effective quality decision activities.

To compile this literature review, a search was conducted electronically to locate all relevant literature written in English, primarily peer-reviewed scholarly journals, through various databases, including CINAHL, Embase, Emerald, Google Scholar, Medline, ProQuest, PsycNet, PubMed, and PDA Technical Reports, Science Direct. Other applicable information (i.e., professional organizations and administrative reports) was gathered using Google and Google Scholar search engines. Resources include journal articles, books, government websites, professional association websites, and dissertations.

The key terms utilized in the literature search are: Risk Assessment, Risk-based Triage for Drug Shortages, Risk Communication and Monitoring, Risk Identification, Risk Mitigation, Risk Priority Level, Risk Management, QRM gaps, QRM Maturity. Variations of the key terms were utilized to ensure complete search results. The search scope was from 2009 to 2024, integrating pertinent seminal works and most literature used in the review was published between 2018 to 2023

### **Quality Risk Management in Cell and Gene Therapy**

Quality Risk Management (QRM) has become a critical component of modern business operations, particularly in highly regulated industries like pharmaceuticals and healthcare, where potential risks to product quality and patient safety are paramount. This literature review examines key concepts in QRM, including risk identification, assessment, mitigation strategies, and the implementation of effective QRM frameworks, highlighting current research gaps that the proposed study aims to address.

In the last decade, attempts have been made to apply QRM predominantly in the healthcare industry (Samardelis and Cappucci, 2009; Agoston et al., 2011), pharmaceutical manufacturing (Liebowitz, 2011; Lopez et al., 2010) while relatively little efforts have been noticed in other industries like dairy (Noordhuizen & Cannas, 2008, Noordhuizen & Cannas, 2009) and construction (Ghezavati et al., 2013). (Samardelis and Cappucci, 2009) conducted a case study which demonstrates the application of QRM strategy to maintain compliance. The outcome of the case study of applying QRM in supplier selection, evaluation and control in blood supply chain (Agoston et al., 2011) strongly suggests that QRM can be a valuable component of an effective quality management system by providing a proactive approach for identifying and controlling potential quality and safety issues

throughout the blood supply chain. This literature review highlights QRM case studies that illustrate how QRM was applied in the development of CGT drug products and used in Production. The studies convey a strong message that Knowledge Management and QRM begin in Product Development and continues through a product's life cycle and concludes that QRM is integral to executing an effective control strategy and maintaining the product. (Lopez et al., 2010) used the QRM approach in cell therapy manufacturing wherein a QRM model is developed using FMEA, AHP, Pareto chart etc. (Noordhuizen & Cannas, 2008, Noordhuizen & Cannas, 2009).

Moreover, adopting mature quality management practices supports a more reliable drug supply chain by reducing the occurrence of quality-related failures and improving the ability of establishments to maintain performance during expected and unexpected supply chain disruptions. Integrating business and manufacturing operations with quality practices and technological advancements can help achieve higher levels of maturity. This can optimize manufacturing process performance and product quality, enhance supply chain reliability and foster proactive continual improvement. The next critical step in implementing this program is developing the protocol that assesses the QMM of manufacturing establishments. This prototype assessment protocol will be tested and refined in section 2.

Moreover, the causal relationship between the various quality risk factors and quality performance has not been adequately studied in previous research studies. Thus, a comprehensive framework of PQRM is assessed, with an intent to enable academicians and practitioners to gain a better understanding of the causal relationships among them. In seeking to

help address the above gaps, this research put forward an innovative PQRM model to examine QRM models.

### **Quality Issues in Manufacturing**

Quality issues in the drug manufacturing process may have serious consequences for patients, prescribers, and consumers. Øyri (2024) indicates that the recent drug shortage in the American healthcare industry, particularly in the wake of the 2020 COVID-19 pandemic, serves as a stark illustration of the impact of quality issues in drug manufacturing processes. Currently, vital medications that are critical to treating life-threatening conditions are either unavailable or in severely limited supply. The majority of these shortages have arisen from deficiencies in drug manufacturing quality, thereby bringing this issue to the forefront. As such, it is crucial to emphasize robust quality management practices to ensure a dependable drug supply chain, mitigate quality failures, and improve performance during disruptions. By integrating business and manufacturing operations with advanced technology, companies can drive maturity, enhance manufacturing performance, elevate product quality, and strengthen supply chain reliability while fostering continual improvement. Those that prioritize advancing their risk management practices will gain a deeper understanding of supply chain complexities, implement robust cybersecurity measures, and optimize inventory management, empowering them to navigate unexpected challenges with success

### **Scope – Role of CDMO in CGT**

For developers engaged in the rapidly evolving domain of cell and gene therapies (CGT), a significant and multifaceted bottleneck lies in the intricate process of translating innovative cell and gene therapy concepts into effective treatments that are both scalable and manufacturable. This transformation is not merely theoretical in nature; it is essential for obtaining regulatory

approvals, ensuring product consistency, and ultimately achieving commercial success in a highly competitive market. The complexity of this endeavor is particularly pronounced within the CGT sector, where the intersection of advanced biological techniques and manufacturing processes requires a comprehensive understanding of both disciplines. Moreover, this challenge is compounded by the notable scarcity of professionals who possess the specialized knowledge and skills necessary in both biological sciences and process engineering, thereby necessitating a concerted effort to cultivate a workforce capable of meeting these demands.

As such, Contract Development and Manufacturing Organizations (CDMOs) have proven their ability to address these diverse and complex needs effectively. The landscape of CDMOs is characterized by evolving regulatory requirements and stringent deadlines imposed by investors, which demand agile responses from these organizations. As companies aim to expedite their clinical trials and commercial launch timelines, an increasing number are choosing to partner with start-up CDMOs that often provide more flexible and innovative solutions.

These start-up CDMOs offer a comprehensive range of services throughout the drug product manufacturing process. By leveraging their expertise, companies can assess capital expenditures thoroughly and identify opportunities to reduce costs without sacrificing quality. This collaboration facilitates detailed evaluations of each phase of the manufacturing process, ensuring that companies can address critical inefficiencies and streamline operations.

Furthermore, CDMOs excel at identifying significant value-added modifications that can enhance product development. They can recommend structured and phased programs that encompass drug development, manufacturing optimization, and regulatory compliance, guiding companies through each stage of the process. Ultimately, partnering with CDMOs not only helps

meet immediate production needs but also supports long-term strategic growth and innovation within the pharmaceutical landscape.

### **Start-Up CDMO Quality Agreements: Client Focused vs. Patient Centered –**

Start-Up CDMOs must work to gain proficiency in clinical batch manufacturing, becoming more relevant in clinical development and provide flexibility in the face of high changeover and portfolio shifts. Price is a priority topic when a client decides to work with a CDMO – however clinical development that is patient centered needs to also be appropriately assessed, planned and budgeted. Building a scalable business requires a continual assessment of structure, resources, systems, space, capabilities, capacities, and technologies. One key is having the technical depth and the ability to meet tight timelines, along with the expertise to scale in a complex environment. Customizing the management of manufacturing methodologies to individual client needs means ensuring regulatory and quality requirements are met and risks are mitigated. Being a client-centric CDMO is critical to ensuring every project – large or small – receives focused attention and specialized handling. It's an approach that transforms potential challenges into successful outcomes. However, since the outcome involves patients and their needs, then it is imperative to ensure processes are monitored in real-time with process inefficiencies either reduced or eliminated. CDMOs are renown for cutting costs and operating within tight budget constraints. Therefore, niche supplies are used during their manufacturing process, which tend to have distinctive characteristics and novel delivery methods that ultimately lead to one-of-a-kind regulatory hurdles.

A prime example, is the use of specific glass fill material for pipettes that are used during the drug manufacturing process. This range of glass materials includes premium and standard options, with the standard being the most affordable choice on the market. However, there have

been instances at Start Up X where the cheaper standard glass pipettes were used in manufacturing to save costs for the client. Unfortunately, this resulted in glass delamination during the final filling of the drug product intended for infusion into a cancer patient. This is an overarching serious concern for parenteral drug products. Over the past several years, there has been a series of product recalls involving glass delamination in parenteral drugs stored in vials which has led to heightened industry and regulatory scrutiny. In Zhao's (2014) study, Non-siliconized syringes were used in order to directly compare glass to glass performance between vials and syringes. The vial and syringe performance was screened with pharmaceutically relevant formulation conditions. The influence of pH, buffer type, ionic strength, and glass type and source was evaluated. In addition, an aggressive but discriminating formulation condition was used to ascertain the impact of syringe processing.

Advanced analytical tools including inductively coupled plasma/mass spectrometry, scanning electron microscopy, atomic force microscopy, and dynamic secondary ion mass spectroscopy showed significant differences in glass performance between vials and syringes. Pre-filled syringes outperform vials for most tests and conditions. The manufacturing conditions for vials lead to glass defects, not found in pre-filled syringes, which result in a less chemically resistant surface. The screening methodology presented in Zhao's (2014) research work can be applied to assess the suitability of cheaper glass supplies for use in specific drug manufacturing processes.

This is due to the fact that, depending on the quality of glass used, pipettes that are incompatible with a drug product can have a significant impact on its stability, where elevated impurities and leachable inorganic elements may be observed, affecting its CQAs, resulting in a suboptimal product with reduced safety and efficacy for the patient. As such, it is imperative to

continue to evaluate policies and related guidelines on drug containers to ensure manufacturers use containers that are appropriate for their specific operations, formulations, and labeled storage conditions, as a patient-focused outcome is the priority.

Therefore, a QRM (Quality Risk Management) approach to selecting the right materials in drug manufacturing is necessary to systematically evaluating potential risks associated with raw materials, considering factors like purity, stability, source, and potential contaminants, to proactively identify and mitigate any quality issues that could impact the final drug product, ensuring patient safety throughout the manufacturing process. Astute quality improvement initiatives are crucial in this context, striking a balance between cost-effectiveness, budget adherence, and maintaining the quality of the end product while continuing to provide safety to patients.

### **Evidence-Based Quality issues in Drug Manufacturing and impact on patients**

It is widely agreed that pharmaceuticals should be manufactured to a high standard of quality, because they are frequently critical to human health, and because the consequences of quality problems such as sub-potency, lack of sterility, or product mix-ups can be so devastating, Nevertheless, the U.S. Food and Drug Administration (FDA) continues to see major problems in pharmaceutical manufacturing. In addition to the costs of recalls and lost sales, manufacturing facilities often must be shut down for remediation, prolonging the gap in production. Some firms may even lose the ability to access the U.S. market. There also can be serious reputational consequences for companies that must recall their products and then are unable to supply their customers for an extended period.

Manufacturing problems also may have serious consequences for patients, prescribers, and consumers. Bitan (2024) postulates that the most egregious quality problems at drug

manufacturing facilities include mold in vials of medications and metal shavings in bottles. As a matter of fact, the persistent issue of drug shortages in the United States, which poses a significant threat to public health and national security, can be primarily attributed to challenges in maintaining product integrity. These challenges stem from inadequate adherence to good manufacturing practices and a deficiency in fostering a culture of quality. Deterioration in product quality is often linked to various factors, including the utilization of aging facilities, the necessity for companies to share production facilities for new products, insufficient oversight in contracting practices, and intensified price competition. Drug shortages in healthcare facilities can compromise patient outcomes by causing delays or even cancellations in inpatient medication treatment, outpatient infusions, immunizations, and medical procedures.

The recent drug shortage crisis exemplifies one set of consequences. For decades, the health care community and patients have taken the traditionally high-quality, reliable U.S. drug supply for granted. Currently, some essential drugs needed to treat life-threatening conditions are unavailable or in very short supply. The clinical community has been shocked by this situation. Congress, the Administration, and the media have expressed a tremendous amount of anxiety and concern about drug shortages. Many of these shortages have been driven by drug manufacturing quality failures, bringing this issue into the spotlight. Shortages of essential drugs can result in serious health consequences, as patients' treatments may be delayed, or physicians may be forced to use a less desirable alternative, for example, cancer therapy. Less commonly, drug quality problems may directly lead to adverse health consequences, for example, when a patient receives the wrong drug due to a mix-up in packaging.

The main goal in managing drug shortages is to prevent harm to patients. It is important to ensure that all patients receive the medications they need to manage their medical condition

whenever they need them. The risk of potential drug shortages should be considered when making decisions regarding the supply and manufacture of drug products and their active substances. MacGillivray (2020). This project aims to address how drug shortages caused by manufacturing and quality issues can be anticipated and avoided using a risk-based approach at a product level. Drug product manufacturing facilities should establish a comprehensive program to continually monitor their process performance and the quality of their drug products.

### **QRM Definition and Conceptual Framework**

#### **Industry-Specific Applications:**

**Pharmaceutical Industry:** The application of ICH Q9 guidelines for QRM in drug development, focus on the assessment of potential drug-related risks and the development of risk management plans. Quality Risk Management (QRM) is a systematic process for identifying, assessing, controlling, and communicating risks to the quality of a pharmaceutical product throughout its lifecycle. QRM is a vital part of good manufacturing practices (GMP) and is essential for ensuring that pharmaceutical products are safe, effective, and high-quality. This comprehensive process encompasses the regulation and review of quality-related risks. It holds particular significance within the pharmaceutical sector, where product quality significantly influences patient health and safety. In the fast-paced and tightly regulated realm of biopharmaceutical manufacturing, the maintenance and assurance of quality stand as pivotal determinants of success. A robust QRM system constitutes a cornerstone within the overarching quality management framework of biopharmaceutical organizations. It offers a systematic, scientific, and risk-centered approach to decision-making, effectively addressing potential quality concerns during the manufacturing process. High-performing organizations adeptly

integrate QRM into their comprehensive quality policies and procedures to refine and expedite decision-making processes.

The aim of this research paper is to evaluate a more targeted approach for enhancing existing quality risk management (QRM) methodologies, particularly within a start-up CDMO pharmaceutical company. In the context of a start-up Biopharmaceutical company, it is imperative to scrutinize the efficacy of their current QRM system in adherence to good manufacturing practices within the framework of the bench-to-bedside medical treatment continuum, with an unwavering focus on prioritizing patient welfare. As such, it is crucial for biopharmaceutical companies to adopt QRM, but there are notable variations in the regulatory demands and interpretations of QRM. Regulators frequently have divergent expectations, and it would be beneficial for the industry to receive further guidance, as the absence of clear directives presents a significant challenge in implementing QRM. It is essential for individuals involved in applying QRM principles to have a deep understanding of QRM in order to appreciate its benefits and ensure its sustainability after implementation. While training is crucial for QRM, it primarily imparts basic concepts for task execution. What is truly necessary is the establishment of a framework for delineating and enhancing individual QRM maturity. This entails defining the responsibilities of each QRM role and identifying the required competencies to foster individual QRM maturity.

Hence, a robust quality performance plan ensures that current processes are effective and validated by assessing baseline process performance. Additionally, it identifies early indicators of atypical process performance and recommends quality improvement practices. To ensure regulatory compliance, systematic evaluations, such as a root cause analysis of current quality control processes throughout the lifecycle of drug product manufacturing to drug product

delivery to patients via hospitals, pharmacies, and other healthcare providers, are imperative. Xyrichis (2021). Drug Product manufacturers remain responsible for developing strategies to mitigate supply-chain issues, which requires careful assessment of Key Performance Indicators along with collaborative interactions among stakeholders. This comprises fundamental interaction among logistics, manufacturing, packaging/ labeling, quality-control testing, product release, and distribution teams so as to provide maximum assurance of an ongoing supply of pharmaceutical products. Wang, Grundy, Parker, & Bero. (2020)

As such, it is essential to address quality issues such as product quality, regulatory compliance, supply chain management, data integrity, counterfeit medicines, adverse event reporting, technology adoption, research ethics, and product labeling; doing so will empower drug manufacturing companies to further their impact on advancing global health and well-being. These quality improvement initiatives are representative of the standards and practices that manufacturers must meet regarding the facilities, controls, and methods used to manufacture, hold, process, or package drug products. Shenoy (2021).

The FDA continues to respond to poor manufacturing practices via compliance and enforcement actions, but clearly the responsibility for maintaining quality rests squarely with the manufacturers themselves. In response to this ongoing cluster of problems, it may be time to step back and try to uncover the root causes of this seemingly intractable issue. The widespread and successful adoption of six sigma and related quality management techniques in other manufacturing sectors would imply that reliable, high-quality manufacturing is also attainable in the pharmaceutical sector. Moreover, the Pharmaceutical Regulatory Science Team (PRST), a research team based at the Dublin Technological University (TU Dublin) in Ireland, recently conducted a Quality Risk Management (QRM) survey and a face-to-face focus group workshop

to assess the level of formality of QRM roles in the biopharmaceutical sector. This was carried out as part of Waldron's (2017) research study, which identified the need for the development of QRM role-based competencies as fundamental to realizing QRM's benefits. The research study followed a hybrid methodology composed of: (1) Survey 1, (2) focus group workshop, (3) Survey 2, and (4) competency model development.

Moreover, Quality risk management (QRM) is now a regulatory expectation, and it makes good business sense. The goal of the risk assessment is to increase process understanding and deliver safe and effective product to the patients. Risk analysis and management is an acceptable and effective way to minimize patient risk and determine the appropriate level of controls in manufacturing. While understanding the elements of QRM is important, knowing how to apply them in the manufacturing environment is essential for effective process performance and control. This article will preview application of QRM in pharmaceutical and biopharmaceutical manufacturing to illustrate how QRM can help the reader achieve that objective. There are several areas of risk that a drug company may encounter in pharmaceutical manufacturing, specifically addressing oral solid and liquid formulations. QRM tools can be used effectively to identify the risks and develop strategy to minimize or control them. Risks are associated throughout the biopharmaceutical manufacturing process—from raw material supply through manufacturing and filling operations to final distribution via a controlled cold chain process. Assessing relevant attributes and risks for biotechnology-derived products is more complicated and challenging for complex pharmaceuticals. This paper discusses key risk factors in biopharmaceutical manufacturing.

Successful development and commercialization of pharmaceutical products is all about managing risks. If a company was to take zero risk, most likely the path to commercialization

would not be commercially viable. On the other hand, if the risk taken was too much, the product is likely to have a suboptimal safety and efficacy profile and thus is unlikely to be a successful product. This article addresses the topic of quality risk management with the key objective of minimizing patient risk while creating an optimal process and product. Various tools are presented to aid implementation of these concepts.

### **Evidence of ICH guidelines on CGMP**

Drug substance development and manufacturing operations are undergoing changes with the implementation of ICH Q7, Q11 and process validation lifecycle guidance requirements. This requires specialized quality risk management considerations due to the diverse nature of attributes that need to be considered at the various lifecycle phases. Waldron's (2017) research proposes a roadmap for implementing end to end quality risk management tools at drug substance development and manufacturing organizations. That guideline should aid in incorporating the quality risk management principles into this dissertation's assessment of a quality management system for routine use and risk mitigation activities. The use of statistical tools and visualization tools is also important during QRM activities to decipher potential risks. Routine management risk review and communication are important elements of the QRM process to ensure that the residual risk is addressed in a timely fashion to reduce the impact on patients and increase personnel safety and product. As such, a tailored approach is required for quality risk management (QRM) in drug substance development and manufacturing than drug product due to the difference in processes and control strategies. The purpose of a roadmap is to articulate the areas of QRM application and identify the tools that are "fit for" drug substance manufacturing which should help in standardization. Developing a QRM approach for a drug substance is of particular interest for the industry as there are more percentage of warning letters

being issued to drug substance manufacturers. ICH Q7 allows for phase appropriate application of cGMP's however provides no directive, further requiring extensive adoption of QRM approach in drug substance manufacturing.

The ICH Q7 good manufacturing practice (GMP) guidance<sup>1</sup> for active pharmaceutical ingredients (API) stipulates the basic GMP requirements involved in drug substance manufacturing from introduction of starting materials to processing and packaging. The guidance cover personnel, facility, equipment, material, manufacturing, laboratory, storage, laboratory, validation, change and quality management controls sections. ICH Q7 excludes vaccines, blood, plasma derivatives, radiopharmaceuticals and gene therapy pharmaceutical ingredients. API manufacturing utilizes designated starting materials (RSM), intermediates and raw materials at various steps, where some of the building block raw materials are commercially available. The API manufacturing segment differs from drug product GMP operations. API manufacturing has early stages of manufacturing building blocks for key steps and developing case by case rationale to determine the correct starting point of API manufacturing. ICH Q7 has attempted to clearly break down the requirements, for example, for a chemical synthesis.

The controls for API and intermediate manufacturing should be phase appropriate and in line with the stage of drug substance development. The guidance on development and manufacture of drug substance (ICH Q11) is relatively new, published in 2012.<sup>2</sup> There are very few regulatory inspection compliance citations specific to the guidance at this time, in comparison to the well-established drug product Quality by Design (QbD) concepts (ICH Q8). The Q11 guidance and associated Q&A provide details on a QbD approach to drug substance process development, justification of starting materials, lifecycle process validation and Quality

Risk Management (QRM). This article outlines the application of QRM throughout the stages of drug substance manufacturing and the methods to apply the ICH Q9 risk management principles.

### **Manufacturing Process**

Depending on the developed synthetic route, manufacturing operations have associated isolation and purification steps. Reprocessing by recrystallization, distillation, filtration, column chromatography, milling etc. are a general part of the manufacturing process. Mother liquor recovery of reactants, intermediates and API are performed as per the approved process and quality is confirmed prior to use. The reaction, crystallization and drying processes require management of bulk material quantities. Evaluation of safety and scale effects on the selected equipment train are therefore important for successful commercialization. Special considerations need to be in place for the use and traceability of the recovered material. Cross contamination controls are of particular importance when non-dedicated equipment such as reactors are utilized in the various steps. A robust cleaning validation and verification program with validated test methods is critical to ensure minimal carry over. Addressing these requirements is challenging for newly developed API synthetic routes, as the chemistry and process understanding is not well established. Validated/verified laboratory test methods are required for characterization at all development stages, raw material testing, registered starting material testing, intermediate material testing, final API testing, stability testing and in process testing. In-process control (IPC) testing of intermediate and API manufacturing encompasses assay, purity, water content etc. to determine adequacy of material quality at various stages. In some cases, the reaction continues while the IPC results are generated for further charging calculations.

Process Performance Qualification (PPQ) studies therefore warrants careful planning and risk assessment. The subsequent Stage 3 Continued Process Verification plan for drug substance

needs to consider monitoring of processing loops and variables such as drying, reaction time etc. Drug substance intermediate and final manufacturing steps need to consider the input variables. Some intermediate steps may be independent of the previous steps. In most cases the quality attributes establish reaction end point and therefore minimal data may be available to determine within batch variability. Continued evaluation of evolving risks are hence important in drug substance manufacturing to enhance the control strategy. A preliminary risk categorization is the first step towards implementing QRM principles in drug substance manufacturing.

The drug manufacturing process for chemical entities involves synthetic route development and process development to enable successful chemical reaction conversion mechanisms. In some cases, it may involve numerous chemical conversions in multiple process steps to produce few grams of highly potent active pharmaceutical ingredient. The manufacturing process can extend to months. Process design becomes an important aspect of drug substance development and scale up for commercialization. Each drug substance manufacturing process is unique, depending upon complexities such as number of chiral centers and reaction mechanisms. Product yield, material cost, safety, environmental, quality and process efficiency are important in drug manufacturing and need to be considered as part of process development. However, the possibility of different reaction pathways presents challenges in implementing standard processes. The industry thus has some unique needs and has advanced in certain areas in comparison to drug product manufacturing process. This scenario presents an opportunity to strengthen drug substance operations by identifying and using quality risk management tools at each stage.

## **Phase Appropriate Application of QRM**

Drug Product manufacturing and testing can be divided into five categories and related to the lifecycle stages (Process Validation Stage 1, 2 and 3). The product and patient risk level increases as development moves from its early stages to commercial manufacturing (1-5). Category 1 primarily includes early development study batches to define critical process parameters and for process optimization. The analytical test methods at this stage are non-validated methods. Category 2 and 3 are primarily clinical, registration, stability, and demonstration batches some of which will be utilized for human clinical trials. The only difference between categories 2 and 3 is the use of non-validated analytical test methods versus the use of validated test methods. Analytical test methods, including in-process methods, are typically in validation at this stage. Category 4 batches may be utilized for drug product-formulation development batches, and commercial batches. The analytical test methods need to be fully validated at this stage. Category 5 includes commercial batches undergoing continued process verification. Throughout stages 1-5 the maturity of the risk management tools increases to accommodate the data and product/process knowledge captured throughout the lifecycle of the process.

## **Application of QRM Principles in Drug Manufacturing**

The criticality of Stage 1 includes development principles (ICH Q11), and the unique processing steps that make drug product development and commercialization a distinctive segment. The reaction mechanism and processes, for example the ongoing charging, makes the in-process analysis critical in ensuring attainment of established quality attributes. The drug substance manufacturing operations involve multiple intermediate steps and variables, of which some are dependent and some are independent. Therefore, a tailored roadmap for QRM is

recommended in drug product development. Each of the categories defined requires varying levels of risk assessment and associated tools based on the development phase of the product.

Throughout the product lifecycle, the data collected will be captured and risk assessments will be performed to enable knowledge of the process under assessment. Each stage of the process will utilize a combination of scientific data and risk management principles to ensure process robustness and ultimately ensure product quality. A critical assumption in the execution of these risk assessments is cross-functional involvement, Research and Development is responsible for the synthetic route development validation and transfer; the Quality Unit is responsible for quality control laboratory operations, quality assurance, investigation, annual quality review and compliance; and Technology Operation is responsible for scale up, process transfer. It is the cumulative involvement of all these players that enables a robust risk assessment.

### **Assessment of Evidence Based QRM Application in Manufacturing**

A wealth of literature exists on the subject of QRM in the pharmaceutical and biopharmaceutical industries, encompassing a diverse range of sources such as regulations, regulatory guidance documents, books, industry whitepapers, peer-reviewed articles, presentations from regulators and industry practitioners, as well as commentary and opinion pieces. This involves synthesizing a wide range of resources and journal articles to gain a comprehensive understanding of QRM strategies, as well as the root causes of errors in the drug manufacturing processes, in addition to the adverse patient outcomes. Bitan (2024) postulates that by adopting a quality systematic approach that emphasizes patient safety and improving health outcomes, it becomes possible to address the intricacies of modern healthcare more effectively. In today's healthcare landscape, the importance of quality and safety improvement

initiatives cannot be overstated. Such initiatives play a pivotal role in enhancing the likelihood of achieving desired health outcomes and are in line with current professional knowledge. It's worth noting that within the healthcare sector, most manufacturing deviations stem from poor quality processes rather than being attributable to individuals. Factors such as inefficient and variable processes, changes in patient case mix, variations in health insurance, disparities in provider education and experience, and numerous other elements contribute to the inherent complexity of healthcare.

As such, this literature review presents various perspectives that highlight the evolving understanding of QRM, a crucial aspect of research. Where relevant, the researcher has provided a thorough evaluation of conceptual advancements, thought leadership, and limitations.

Moreover, the evidence obtained from literature that was reviewed are applicable to QRM strategies, the drug manufacturing process, and challenges faced by start-up CDMOs, which all highlighted the objectives of healthcare reform, national endeavors to establish a culture of quality and safety, the principles of quality improvement, and how these principles can be applied in patient care and medical practice.

### **Assessment of current QRM Approaches across the Pharmaceutical Industry - Emerging Trends and Research Gaps:**

**Integration of Data Analytics:** Recent research by Waldron (2017) and [Sharma, 2018] explores the potential of advanced data analytics tools to enhance risk identification and assessment, enabling proactive risk management. Waldron was effective in delineating 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. 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 the influence of external assessment on surgeons' reporting. The study delves into the intricate experiences of surgeons operating within the Norwegian healthcare system and examines how they are impacted by external assessment and scrutiny from regulatory bodies. It uncovers the multifaceted impact of such external assessment, revealing that it can elicit both positive and negative effects on surgeons' reporting and learning processes. On one hand, it may lead to the unjust criminalization and scapegoating of surgeons, potentially impeding efforts to improve quality and safety within the healthcare system. Conversely, it has the potential to inspire surgeons to adapt and refine internal procedures and routines in response to external scrutiny. The prioritization of transparency regarding adverse events by the government underscores the significance of external feedback to healthcare providers as a crucial element in enhancing services and mitigating adverse events.

**Organizational Culture and Leadership:** Sharma (2018) highlights the importance of a strong organizational culture that supports open communication and risk ownership for successful QRM implementation. Sharma (2018) emphasized the need to promote a strong culture of quality, recognize establishments with robust quality management practices, and provide support and recommendations for areas where quality management practices can be enhanced. Sharma's (2018) research iterates that through effective QRM programs, industry assessors can work together to drive proactive continual improvement in the pharmaceutical industry. Furthermore, an examination of Sharma's (2018) literature on quality management uncovered existing programs that evaluate elements of quality culture on pharmaceutical quality, surveying external

stakeholders and gathering feedback from partner offices and centers within the FDA. This provided valuable insights into the content of the practice areas and the scientific aspects of performance measurement.

**Quantitative Risk Assessment Methods:** While qualitative risk assessment methods are widely used, as explored by Waldron, there is a growing interest in developing more robust quantitative risk assessment models, as explored by O Donnel (2012). Waldron's (2017) qualitative research, based on in-depth interviews with 15 surgeons from four Norwegian university hospitals, sought to comprehensively explore the impact of assessment by external bodies on transparency, reporting, and the learning process following serious adverse events. The external bodies encompass external inspection, internal police investigation, patient injury compensation systems, and media. The study's findings shed light on how external assessment can create a dichotomy between medical perspectives and external regulatory perspectives, potentially acting as a barrier to the ongoing efforts to elevate quality and safety standards within the healthcare system.

Another research article by O'Donnel (2012), presents a practical way in which current approaches to quality risk management (QRM) may be improved, such that they better support qualification, validation programs, and change control proposals at manufacturing sites. The paper is focused on the treatment of good manufacturing practice (GMP) controls during QRM exercises. It specifically addresses why it is important to evaluate and classify such controls in terms of how they affect the severity, probability of occurrence, and detection ratings that may be assigned to potential failure modes or negative events. It also presents a QRM process that is designed to directly link the outputs of risk assessments and risk control activities with qualification and validation protocols in the GMP environment. This paper concerns the need

for improvement in the use of risk-based principles and tools when working to ensure that the manufacturing processes used to produce medicines, and their related equipment, are appropriate. Manufacturing processes need to be validated (or proven) to demonstrate that they can produce a medicine of the required quality. The items of equipment used in such processes need to be qualified, in order to prove that they are fit for their intended use. Quality risk management (QRM) tools can be used to support such qualification and validation activities, but their use should be science-based and subject to as little subjectivity and uncertainty as possible.

### **QRM Maturity: Assessment of QRM Maturity in Current Manufacturing Processes**

The primary objective of the research outlined in Waldron's (2017) dissertation was to delineate the stage of QRM implementation maturity necessary to safeguard patients from the risks associated with low-quality medicinal products. The research was conducted in three phases, with three primary objectives: evaluating patient protection after the publication of ICH guidelines, assessing the maturity of QRM within the industry, and focusing on developing a mature QRM program and suitable tools for improvement. However, Waldron's (2017) research concluded that there has been no significant improvement in patient protection since the implementation of QRM, and the level of QRM maturity in the pharmaceutical and biopharmaceutical industries remains relatively low. Nevertheless, the research also suggested that transitioning to the more mature QRM model proposed in Waldron's thesis may enable companies to conduct QRM more effectively, ultimately leading to improved risk management for patients.

As such, this dissertation paper aims to focus on the elements that a robust QRM system canopies at a Start-Up biopharmaceutical company – particularly Good Manufacturing Practices and this dissertation paper will explore the key components of how organizations effectively manage information to ensure QRM maturity, accuracy, accessibility, and reliability across different formats. Additionally, Waldron's (2017) review examines the ability of biopharmaceutical organizations to synthesize information from various sources, propose suitable solutions, and ensure their successful implementation to improve business operations and production processes. It is essential to note that Biopharmaceutical companies without well-established Quality Risk Management (QRM) processes may struggle to effectively integrate data, hindering their ability to conduct thorough analyses and gain valuable insights into their operations and potential quality-related risks. This limitation can impede their capacity to identify opportunities for improving production and business processes. In contrast, Biopharmaceutical companies that have a more mature QRM process in place can leverage relevant data and knowledge, allowing them to optimize both production and business operations. Despite having financial resources, Biopharmaceutical companies that lack mature QRM systems may be hesitant to embrace changes, whether technological, procedural, or conceptual, that could enhance their operations. On the other hand, Biopharmaceutical companies that have a more mature QRM process are open to evaluating and adopting changes that have been thoroughly evaluated and can bring value to their operations while minimizing associated risks.

Moreover, Waldron's (2017) research commenced with a review of the extant literature. The literature serves as a consistent element of the research design and the thesis clearly 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, Pharmaceutical Development, Quality Risk Management, and the Pharmaceutical Quality System. Waldron's (2017) review examines the ability of biopharmaceutical organizations to synthesize information from various sources, propose suitable solutions, and ensure their successful implementation to improve business operations and production processes. Waldron's (2017) research study evaluated 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.

Furthermore, it is crucial to embrace mature quality management practices to bolster a more dependable drug supply chain by minimizing quality-related failures and enhancing establishments' capacity to uphold performance during anticipated and unforeseen supply chain disruptions. The integration of business and manufacturing operations with quality practices and technological advancements can facilitate the attainment of greater levels of maturity. This, in turn, can optimize manufacturing process performance and product quality, improve supply chain dependability, and promote proactive continual improvement. As such, the case study on Waldron's (2017) dissertation highlighted the criticality of patient quality and safety for biopharmaceutical companies: it assessed comprehensively the research question, the structure of the research effort, and the research methods to be employed. Moreover, inexperienced biopharmaceutical companies may not fully grasp the complexities and risks within their supply chains, leading to the development of limited risk management strategies that may be ineffective in handling unforeseen disruptions. On the other hand, biopharmaceutical companies that

prioritize the maturation of their risk management practices will gain a comprehensive understanding of the complexities and risks in their supply chains, implement robust cybersecurity measures, devise effective risk management plans, anticipate demand, vet alternative suppliers, and optimize inventory levels. This strategic approach enables them to adeptly navigate unexpected disruptions.

### **Summary of the Evidence:**

In a study conducted for quality risk management of pharmaceutical and biopharmaceutical industries in 2017 and 2018 revealed that although substantial progress is made by pharmaceutical companies however, complete adoption of quality risk management techniques are not employed. These companies are nearly halfway in the direction of achieving complete maturity of quality risk management. (Waldron K, 2017, p.330-345). Effective quality risk management strategies which investigates the potential root cause of the quality risk management issues using tools such as fish-bone diagram (Ishikawa), 5-Whys, FTA etc. will allow the companies to identify strengths, weaknesses, opportunities and threats of the projects. The adequate planning for uncertain events can make the companies ready for them whenever they arise. Using the above-mentioned techniques can ensure the success of the project and help the companies to define how potential risks can be identified. Once these potential risks are noted, the companies can design the risk management plan accordingly. Successful managers of projects always acknowledge that management of risk is vital, since accomplishing a project's objective and goals is dependent on preparation, execution, outcome and assessment which may to achievement of strategic objectives.

Moreover, effective risk management approaches permit the companies make the most of revenues and diminish the expenses on events which do not generate enough profit on

investments. The detailed analysis of the risks may help project managers to plan and prioritize their work on the bases of the outcome of each step in the project. (Duggan, 2017). Additionally, though health authorities frequently assess risks and benefits of any new drug during drug approval process, however, they do not typically complete quality risk benefit assessment nor is it accessible in a reliable and integrated framework when it is used. The presently used traditional process does not produce an clear, reliable, transparent, and cumulative quantification of the risks and lacks precision pertaining to the role of specific factors in the approvals. This does not permit the organized reassessment of risks over time. Therefore, the purpose of this literature review is to identify and describe the potential root cause of the quality risk management issues on Startup CDMOs in the pharmaceutical industries. Moreover, based on the exhaustive literature evaluation, this research intentions at understanding the extent of acceptance, absorption and practice of the project risk management process, tools and techniques in the pharmaceutical segment.

### **Summary of literature findings:**

As discussed, the key aspect of my research is to implement adequate risk management technologies for effective management of drug safety products. In today's time of increasing competition and globalization, project accomplishment has become even more analytical to measure the performance of business however, there are still some projects which suffer noncompliance, delays and failures. Currently pharma companies have well developed risk management tool however, still the success rates of projects is not as expected because either the project managers are unaware of use of risk management tools or these tools are misapplied in project planning and execution. (Tzvi Raz, 2002, p. 101-109).

In an empirical study devoted to analyzing use of risk management tools and techniques, data from a Startup CDMO company in the Cell and Gene Therapy Pharmaceutical industry was

gathered and assessed with other QRM data at varying maturity levels within the Pharmaceutical industry. The level of use of risk management traditions were studied using probabilistic risk analysis, risk

documentation, planning and trade-off analysis. In addition to this the variability of impact and application across various projects and their influence on numerous project achievement magnitudes was also studied. The data of this analysis suggested that risk management strategies are not used extensively. Of these literature reviewed, only limited number of projects used very rare and mature risk management practices at Start Ups and most of the projects do not use all the current tools of risk management. The projects using adequate risk management practices were found to be more successful therefore, these practices were related to the success of the project. Tzvi Raz, 2002.

The pharmaceutical industry currently employs wide variety of project management techniques and methodologies for few years, however, its overall development and influence are far behind when compared to other industries. (Byers, 1989, p. 11-12). Largely this is due to the intrinsic complications in managing the research and development projects. The newly developed technologies have inherent unpredictability which makes its necessary to work field of standard approaches to management of project. (Sheasley, 2016, p.37-43).

Drug development is research oriented and highly risky endeavor. Market approval of one drug may take up to screening of 5000 compounds. Each compound may have its own inherent risk factors therefore, substantial resources gets exhausted in the early stages of development. Pharmaceutical companies end up spending around US\$350 to 500 million (including the cost of failed projects) for marketing of one drug. It is very common that drugs fail in prefinal stages of development i.e. phase III of clinical trials. The uncertainties at each step of

drug development necessitates the pharmaceutical companies to execute 40 to 50 projects so that the success of projects can be ensured and new chemical entities could be launched in market. Along with external risk factors there are inherent uncertainties at each step therefore, it becomes very difficult to be sure that the new drug will be as successful as desired or planned. The competitors in market may also launch comparators or comparable drugs during same time or unforeseen noxiousness may lead to withdrawal of drug from market. (Kaufman, 2002).

**Strengths: Summary of robust findings on QRM evidence and risk management strategy maturity on quality of CDMO manufacturing processes.**

Embracing mature quality management practices plays a crucial role in strengthening the reliability of the drug supply chain. By actively reducing the incidence of quality-related failures, these practices help ensure that products meet safety and efficacy standards consistently. Furthermore, they enhance an organization's capability to maintain optimal performance levels during both anticipated disruptions—such as seasonal fluctuations in demand—and unexpected challenges, including natural disasters or raw material shortages.

The integration of business operations with manufacturing processes is vital. By aligning these efforts with established quality practices and leveraging the latest technological advancements, companies can achieve significant improvements in their operational maturity. This holistic approach not only streamlines manufacturing processes but also elevates product quality, minimizing waste and inefficiencies.

In addition to optimizing performance, adopting these comprehensive quality management practices bolsters supply chain reliability. This means that companies can trust their systems to deliver consistent results, fostering stronger relationships with stakeholders, including suppliers and customers. Most importantly, a commitment to continual improvement encourages

organizations to proactively identify opportunities for enhancements, ensuring that they can swiftly adapt to changing market demands and evolving regulatory requirements. Through this proactive stance, companies can drive sustainable growth and maintain a competitive edge in the pharmaceutical industry.

The authors revealed that QRM tools are designed to transform data into knowledge in an objective and transparent manner, thereby enhancing the overall quality of decision-making and risk management. Each QRM tool possesses distinct characteristics that influence how risks are identified, how data is entered, how information is processed, and how outputs are generated. By crafting a well-defined risk question and understanding the types and quantities of supporting data available, QRM tools can be strategically selected to ensure compatibility with the study data and to effectively deliver a cohesive risk control plan. The choice of which tool to utilize is crucial, as it can have a significant impact on the usefulness, ease of execution, quality, and even validity of the risk assessment. A thoughtfully selected QRM tool streamlines the risk assessment process, emphasizes the strengths of existing risk controls, and processes and conveys data in a clear and comprehensible manner. It may even unveil previously unknown risks. Well-chosen tools will naturally prompt user inputs and pose questions in a way that is immediately intuitive for the risk assessment team.

An advanced Pharmaceutical Quality System (PQS) employs a comprehensive and systematic methodology for assessing, controlling, communicating, and reviewing the various risks associated with the quality and availability of drug products throughout their entire lifecycle. This approach encompasses all stages, from initial development and manufacturing to distribution and post-market surveillance. This literature review has established that one of the core principles of an effective PQS is adopting a proactive stance on Quality Risk Management

(QRM). This means that organizations actively seek to identify potential risks before they escalate into significant issues. By integrating QRM into their processes, companies can significantly diminish the likelihood of quality-related failures. This proactive mindset is essential to maintain not only the integrity of drug products but also the safety and satisfaction of patients relying on these medications.

In contrast, less mature organizations often adopt a reactive approach, focusing primarily on implementing corrective actions only after a failure has occurred. This tendency can lead to a cycle of continual problem-solving without addressing the root causes, ultimately overlooking preventive measures and strategies that could address potential issues proactively. Such an approach can expose the organization to substantial risks, including compromised product quality, regulatory penalties, and damage to their reputation. In stark contrast, more mature organizations recognize the importance of embedding QRM principles within their operational frameworks. They leverage their accumulated knowledge from the entire product lifecycle, which allows them to make well-informed and timely decisions that align with both compliance requirements and overall quality objectives. These organizations prioritize regular reviews of identified risks at defined intervals, promoting a culture of continual improvement within their teams. This ongoing assessment not only enhances the robustness of their PQS but also ensures the consistent availability of high-quality drug products that meet the needs of patients and healthcare providers alike. Through this diligent approach, advanced PQS implementations foster a sustainable environment of quality assurance that is responsive to both current challenges and future developments in the pharmaceutical landscape.

**Weaknesses: Gaps in research, limited sample sizes, potential biases, and lack of longitudinal studies on QRM risk maturity strategies and quality outcomes.**

Previously, some attempts have been made to integrate Risk Management and Quality Management. Maria and Adina (2011) attempted to highlight the links between risk management and quality management and brought up the considerations on integrating Risk and Quality Management. As the QRM concept is relatively new, there is a need to put in more efforts to explore deeper to understand the related/underlying concepts and the associations among them. Furthermore, this Literature review reveals that current QM practices put more focus on the 'Reactive approach' and neglect the 'Proactive approach' in dealing with quality failures. In other words, project teams tend to act on solving quality failures through corrective actions like rework, resubmission, retesting etc., instead of putting efforts in preventing them from happening in the first place through techniques like risk assessment/analysis so that potential risks/causes leading quality failures could be detected ahead for applying preventive actions could potentially avoid quality failures from occurring/re-occurring.

Moreover, Previous Quality Management studies have mostly examined the quality issues/failures, their causes and impact on project objectives in general, in the light of quality management principles and practices. Some studies extended this by studying the causal relationship between quality management practices and quality performance, financial performance, organizational performance etc., wherein the risk factors have been ignored. However, the causal relationship between the various quality risk factors and quality performance has not been studied adequately. Thus, a comprehensive framework of PQRM which reflects the multi-dimensional content of QRM and Quality risks (QR) and Quality performance(QP) is needed for academics and practitioners to gain a better understanding of the measurement and association/relationships among them.

Hence, the traditional QM practices need to be reinforced with Risk Management methodology, which could fill up the gaps related to deficiency in a proactive approach in a holistic manner to reduce quality failures so as to ensure the achievement of quality objectives or enhance quality performance. Although risk management is done, the identification of quality risks is neglected and moreover, the risk assessment scoring is provided absolute value which is very subjective wherein the past trends or data base is seldom referred to. This potentially leads to a very baseless or unreliable risk assessment/evaluation.

### **Implications for this project.**

Poorly chosen QRM tools may make risk assessments frustrating exercises and may reduce the overall effectiveness of risk management efforts. Incompatibilities between the tool, the risk problem statement, and the supporting data may lead to several unintended consequences, including:

- Known risks and unknown (but probable and potentially catastrophic) risks may go unaddressed.
- Significant risks may be underrated, while insignificant risks are overrated; this is especially common when identified risks do not properly fit into the structure or context of predefined rating schemes and “worst-case” or “best case” risk ratings are assigned by default.
- Strengths in risk control may be underemphasized or overlooked, while weaknesses in risk control may be overemphasized.
- Risk assessments may become overly complex and lengthy.
- Misuse of QRM tools may be cited as nonconformance. The validity or usefulness of the risk assessment may be called into question by stakeholders in cases where QRM

tools need to be substantially modified or reinterpreted in order to force-fit the problem statement or data type.

Moreover, an illustrative example includes pharmaceutical manufacturing process hazards analyses. Over the lifetime of a product or process, different tools may be considered in order to leverage available process knowledge into a hazard control plan that is appropriate for the lifecycle stage. For example, process hazard control during early-stage development may be preferably assessed via a simple tool such as Preliminary Hazard Analysis (PHA) as opposed to a rigorous tool such as Hazard Analysis and Critical Control Points (HACCP). During early-stage development, the use of HACCP would likely prove very challenging or even impossible since critical limits for hazard control parameters may not be known or may be rapidly changing. As process understanding evolves through progression into later lifecycle phases, migration of the PHA's elegant outputs into to a HACCP approach may become increasingly feasible and desirable.

With greater process knowledge in hand, more sophisticated and rigorous tools such as HACCP would begin to provide benefits such as the formulation of highly detailed and robust hazard control plans. Such control plans provide the level of specificity and scientific justification that are commensurate with regulator expectations for late-stage development and commercial lifecycle phases. This example highlights the importance of matching the rigor of the risk assessment and its associated tool with both the risk problem statement as well as the phase in the product lifecycle in order to deliver optimal risk management.

### **Introduction to the Precautionary Principle**

The precautionary principle is an essential approach for effectively addressing technological risks, especially in contexts where scientific uncertainties are present. This

principle emphasizes the importance of taking proactive measures to protect both environmental and public health, making it clear that uncertainties or a lack of comprehensive scientific data should not be used as justifications to delay action on known potential risks. As highlighted by Callréus (2005), postponing necessary measures can lead to harmful consequences for human health and the environment.

In situations where there is insufficient scientific information to thoroughly assess the potential risks associated with genetically modified (GM) crops, it becomes even more imperative to implement cost-effective preventive measures. These measures should aim to protect human health and ecological integrity without unnecessary delay. By adhering to the precautionary principle, stakeholders can effectively mitigate the risks posed by GM crops, ensuring that uncertainties regarding their impacts do not impede the adoption of appropriate safety protocols.

Moreover, the precautionary principle is a crucial component of risk management strategies. It assists decision-makers in making informed choices when confronted with potential hazards, particularly in the realm of GM organisms. By embracing this principle, regulators and researchers can navigate the complexities of GM crop risk assessments more effectively, prioritizing precautionary actions that safeguard future generations while fostering innovation and technological progress. The proactive nature of the precautionary principle is grounded in the early detection and assessment of potential sources of uncertainty. This principle highlights the importance of taking preventive measures to avoid harm before fully comprehending the associated risks. It advocates for a concerted effort to minimize risks linked to uncertain outcomes until additional research can reduce or eliminate that uncertainty.

In this framework, the concept of risk is intrinsically tied to the depth and quality of scientific knowledge. Effective risk management can only be achieved when there is a thorough understanding of the relevant factors, enabling informed decision-making based on credible data. By ensuring that adequate knowledge is gathered and meticulously analyzed, stakeholders can draw sound conclusions that guide their strategies for managing and mitigating potential risks. This approach not only enhances safety but also fosters a responsible attitude toward innovation and development

### **Core Components of the Precautionary Principle**

The Precautionary Principle has been used routinely in risk assessment for a very long time, but the concept has been formalized and actively developed since the 1980s. There are different definitions of the Precautionary Principle. One of these includes “activities which are likely to pose a significant risk to nature shall be preceded by an exhaustive examination; their proponents shall demonstrate that expected benefits outweigh potential damage to nature, and where potential adverse effects are not fully understood, the activities should not proceed” (UN, 1982). In a similar but different definition, the application of the Precautionary Principle is called for situations “where scientific evidence is insufficient, inconclusive or uncertain and preliminary scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen by the EU” (European Commission, 2000a).

#### Anticipatory Action

Anticipatory Batching of Pharmacy Compounded Sterile Products.

Timely medication administration is integral to patient care, and operational delays can challenge timely administration. Within an inpatient pharmacy of an academic medical center, intravenous

medications were historically compounded on a patient-specific basis. In 2020, the pharmacy began batching frequently-utilized medications. This analysis explored the impact of compounded sterile batching on pharmacy and nursing services. As such, Medication prescribed in anticipation of symptoms, designed to enable rapid relief at whatever time the patient develops distressing symptoms. Drugs prescribed in anticipation may include previous or current prescriptions, sometimes with a change in the route of administration, and newly prescribed drugs for anticipated new symptoms.

### Proportional Response

The precautionary application of proportionality analysis represents a good balance between two opposing claims: the sufficient protection of fundamental rights during crises on the one hand, and the ability of authorities responsible for averting the crisis to take effective decisions on the other

Proportionality in impact assessments (IAs) and post implementation reviews (PIRs) (“regulatory cases”) is about ensuring the appropriate level of resources is invested in gathering and analysing evidence on the impacts of a policy.

### Reversal of Burden of Proof

A "reverse burden of proof" in health and safety law means that when a company is accused of a health and safety violation, the burden falls on them to prove they took all "reasonably practicable" steps to prevent the harm, rather than the prosecution needing to prove the company was negligent; essentially, the defendant must demonstrate they acted appropriately to avoid the risk, placing the onus on them to show they did everything within reason to ensure safety.

Explanation of the concept where manufacturers must demonstrate product safety rather than regulators proving risk.

- The Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 et seq, authorises the Food and Drug Administration (FDA) to regulate food and drug safety and approve new drugs and medical devices. Among other things, the FDCA prohibits adulteration or misbranding of food, drugs, devices or cosmetics. 21 U.S.C. § 331. The FDA issues regulations (Code of Federal Regulations, Title 21) to ensure safety of products including food, drugs, medical devices, cosmetics and tobacco products.
- The FDCA and subsequent amendments require new drugs and devices to be approved by the FDA through an established process, and authorise the FDA to evaluate these products' risks. The FDA has issued comprehensive regulations governing review and approval of these products (Code of Federal Regulations, Title 21).

#### Public and Stakeholder Involvement

- Importance of transparency and collaboration in risk management.

Partnerships between patient advocacy groups and pharma companies play a unique role in assuring that new medications arriving on the market meet the needs of people with devastating diseases. To both sides, these relationships bring value. For advocacy groups, partnerships provide both capital and information about treatments in the pipeline that may have life-or-death implications. Drug companies gain a window onto the patients' desires, their interactions with doctors and insurers, their willingness to participate in clinical trials and whether they will go to bat for a new drug when it comes to reimbursement and formulary placement.

#### Iterative Monitoring and Revision

- Necessity of ongoing assessment and adaptability in response to new data.

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.

### **Discussion of continuous quality monitoring in CGTs and pharmaceutical QRM.**

Continuous quality improvement (CQI) is a concept in management, health education, and health care delivery through which a group of constituents applies a well-defined methodology to analyze current practices and then implement changes to progress toward a desired performance level. Popular CQI methodologies, such as Lean Management, Six Sigma, Plan-Do-Study-Act (PDSA), and Root Cause Analysis, broadly consist of short cycles of operational change, testing, and evaluation that inform how to sustain long-term improvement in performance, impact, efficiency, and/or extensions to a program's reach.

CQI activities help achieve strategic goals by linking near-term actions to long-term organizational performance and sustained equitable access to health care at the population level.

Maximizing quality has been a long-held goal of the National Institutes of Health (NIH) Clinical and Translational Sciences Awards (CTSA) Program, which has recently required that grant awardees have CQI programs. Awardee sites, also known as hubs, must maintain such CQI programs not merely because they fulfill regulatory requirements but also because they are integral to strategic management processes. Yet even though notices of funding opportunities require that CTSA hubs have a CQI program in place, there is no clear guidance as to what quality or efficiency means, which may limit the ability to achieve high-quality programs.

### **Uses of the Precautionary Principle in Regulatory Guidelines**

#### **Environmental and Public Health Regulations**

*Historical application in environmental protection and public health, focusing on anticipatory measures in uncertain risk scenarios.*

### International Pharmaceutical Regulations

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

Overview of the precautionary principle's integration into regulatory frameworks like the European Union's REACH regulations, FDA guidance, and ICH Q9 guidelines on QRM. Specific regulatory guidelines mandating precautionary measures in CGT manufacturing, including FDA's guidelines for advanced therapies.

### Risk Management in Emerging Technologies

Precautionary guidelines for new biopharmaceuticals and their relevance to CDMO operations:

- Precautionary guidelines for new biopharmaceuticals include extensive preclinical safety testing to assess potential immunogenicity, thorough characterization of the molecule, rigorous manufacturing processes to ensure purity and consistency, close monitoring of clinical trials for adverse events, detailed labeling with potential risks, ongoing post-market surveillance, and regular consultation with regulatory agencies like the FDA to ensure compliance with safety standards. These guidelines aim to minimize potential risks associated with novel biological drugs while maximizing patient benefit.

### **Application of Precautionary Principle to CDMO Manufacturing QRMs**

In the context of this applied dissertation case study, Startup X is a contract development and manufacturing organization (CDMO) that produces cell and gene therapies (CGT), the precautionary principle could serve as an organizational framework for prioritizing patient safety even when the risks associated with these advanced therapies are not fully understood. As reflected in Table 1 below, the application of Precautionary Principle core components to the CGT manufacturing process could guide Startup X in its quality risk management (QRM) strategy to ensure that both client and patient safety are upheld.

**Table 1. Application of Precautionary Principle to CDMO Manufacturing QRMs**

<b>Precautionary Principle Component</b>	<b>Strategy</b>	<b>Example</b>
Anticipatory Action in CGT Manufacturing	Implement anticipatory measures, such as additional quality control testing, beyond baseline requirements.	Retain extra quality samples and conduct stability testing under various conditions, even if not strictly required, could reveal latent product inconsistencies or contaminants that might otherwise go undetected
Proportional Response in Quality Control Measures	Redundancy of testing and quality oversight should be proportionate to level of uncertainty or potential severity of harm.	Apply redundant layers of testing and oversight for early-phase clinical trials where therapeutic efficacy and safety are still being established
Reversal of Burden of Proof	Assume the burden of demonstrating the safety of CGT products beyond regulatory compliance.	Demonstrate transparency in providing detailed documentation of each risk assessment and mitigation step and proactively providing comprehensive evidence of product quality and patient safety to clients across the production process
Public and Stakeholder Involvement	Incorporate both client and patient perspectives through collaborative relationships.	Work with client companies to gather patient feedback from early trial phases can help inform and improve manufacturing processes
Iterative Monitoring and Revision of QRM Strategies	Continuously monitor and evaluate QRM practices.	Risk mitigation strategies are refined based on emerging data, new scientific insights, or feedback from clients and regulatory bodies.

## Summary

In conclusion, this project presents a practical approach to how QRM may be improved so that it better supports qualification, validation programs, and change control proposals in a more scientific way. This improved approach is based on the treatment of what are called good manufacturing process (GMP) controls during those QRM exercises. A GMP control can be considered to be any control that is put in place to assure product quality and regulatory compliance. This improved approach is also based on how the detectability of risks is assessed. This is important because when producing medicines, it is not always good practice to place a high reliance upon detection-type controls in the absence of an adequate level of assurance in the manufacturing process that leads to the finished medicine.

Current quality management practices often emphasize a responsive approach, which frequently neglects the critical importance of pre-emptive strategies in preventing quality failures. Relying on reactive measures can adversely impact other project objectives, leading to increased costs, delays, and a decline in both reliability and credibility. Ultimately, these issues can damage customer satisfaction. To achieve better quality outcomes and maintain customer trust, it is vital to prioritize proactive strategies. Although proactive approaches like internal review of documentation, internal checking/inspection of works using checklists, tool-box talk/training, audits etc., are done, they are mostly done in a random/adhoc manner/caseby-case manner mainly focusing on conformance and rarely consider/take into account, the level of risks associated, for enhancing the efficiency/effectiveness of the QM actions taken.

Assessing specific resources for the dissertation topic that are effective, safe, patient-centered, timely, efficient, and equitable provides a solid framework for developing quality

improvement strategies and tools. The peer-reviewed journal articles that were assessed for the dissertation topic all clearly emphasized the importance of achieving effectiveness and safety through specific process-of-care measures. risks inherent in their supply chains, and therefore, may develop limited risk mitigation strategies that may not be effective in managing unexpected disruptions. Moreover, an overview of the current QM practices including the measurement of quality performance are elaborated, along with the deficiencies in the QRM maturity with respect to failure to control quality failures are presented. Secondly, an overview of the current maturity practices along with its deficiencies in the QRM with respect to failure to control quality risks are explained. Thirdly, the evolution of QRM along with its significance and ongoing trends in implementation are presented. Subsequently, the gaps in the theory and current practices are discussed along with pointing out the way forward with QRM methodology, aimed at enhanced quality performance.

## **Section 2: Method and Design**

### **Statement of Problem**

The management problem is to improve the maturity and robustness of quality risk management (QRM) strategies in the manufacturing process of cell and gene therapies for a startup CDMO. The problem to be addressed in this dissertation project is that the maturity of current QRM strategies being used by Startup X is unknown. Understanding the current level of QRM quality is an important foundation in the development of high quality, mature QRMs that promote both high quality production and manufacturing processes and patient safety practices.

### **Purpose Statement**

The purpose of this applied qualitative case study is to evaluate the maturity of QRM strategies used by a CDMO start up. Understanding the current rigor and robustness of QRM strategies provides allows for the development of higher quality QRMs and the identification of factors that influence the consistency of implementing mature QRM measures for all clients and CGT manufacturing processes.

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The purpose of this applied qualitative case study is to evaluate the maturity of QRM strategies used by a CDMO start up. Understanding the current rigor and robustness of QRM strategies provides allows for the development of higher quality QRMs and the identification of factors that influence the consistency of implementing mature QRM measures for all clients and CGT manufacturing processes.

**PQ1.** What is the current level of maturity of Startup X's quality risk management strategies?

Research strategy for PQ#1: The first research objective is to investigate/evaluate the current level of maturity of Startup X's quality risk management strategies. PQ#1 necessitates the Interview research method which should be adopted for collecting primary data – an exploratory study has been initiated by adopting the interview method using structured questionnaire for collection of primary data.

In the early stage of an exploratory research, where the researcher is seeking guidance, to test ideas, or even to gain ideas about a subject of interest, such approach might be applicable. In this stage of the research study wherein more insights are needed to further move to the next stage of research, the exploratory research (Observation type - Open-ended questions – qualitative analysis of results) approach is chosen, wherein focus is on the discovery of ideas and insights as opposed to collecting statistically accurate data. The objective of the face-to face interviews is to probe specific but dynamic questions that the quantitative survey is unable to address, to allow an understanding professionals' opinions/ perception via open ended questions (Low and Ong, 2014).

**PQ2.** What evidence-based improvements can be recommended to improve the maturity of Startup X's current QRM program?

Research strategy for PQ#2: The research objective here is to review the concepts of maturity as it relates to Quality Risk Management (QRM), Quality Risks (QR) and Quality Performance (QP) to conceptualize and operationalize maturity constructs. As required by PQ#2, Literature review research method is adopted for collecting secondary data. Based on the data types to be collected qualitative research strategy is used.

**PQ3.** What are the primary barriers encountered by Startup X in improving the maturity of risk management strategies?

Research strategy for PQ#3: The third research objective is to evaluate deficiencies in controlling quality failures for organizations with low level maturity and seek suggestions for improvement This involves investigation of the current QRM practices at Startup X with their deficiencies in controlling quality failures and seek suggestions for improvement, development and, testing. Survey research method is adopted for collecting primary data, as well as a case study on Waldron's 2017 research thesis.

A comprehensive evaluation of QRM implementation strategies and tools allows for improved quality control along the pharmaceutical manufacturing supply and distribution chain (Bhagat & Kanyal 2024). With pharmaceutical supply chains extending back to manufacturers all around the world, this assessment aims to gauge the impact of implementing robust QRM quality control measures throughout the manufacturing process, which is needed to protect patients from the risks associated with low-quality medicinal products. According to Frank T et

al. (2008), this can be achieved by conducting thorough product testing and analysis, adhering to Good Manufacturing Practices (GMP) standards, and investing in advanced manufacturing technologies for process optimization and automation. In the pharmaceutical and life sciences industry, maintaining high-quality standards is essential for safeguarding patient safety, ensuring regulatory compliance, and fostering trust and confidence in healthcare products and services. MacGillivray (2020). These techniques involve performance assessment and the use of findings to steer change in current quality standards.

Section 2 presents an overview of the project design that will be used to investigate these project questions. The section begins with a discussion of the project's qualitative exploratory case study design and rationale as to the appropriateness of this methodology to address the project questions. This signifies a characterization of the prevailing state of the Pharmaceutical industry concerning the benefits associated with enhanced patient protection. The overarching goal is to gain a comprehensive understanding of Startup CDMO X's current maturity level, with the aim of implementing a more effective Quality Risk Management (QRM) strategy that enhances product quality and patient safety in comparison to more advanced CDMOs within the pharmaceutical industry. Accordingly, an analysis of the maturity level of QRM at Startup X is undertaken to furnish actionable solutions that aid the industry in assessing and advancing toward the optimal standard. The section continues with a discussion of the study population and sample selection process used for this project and an overview of the proposed data collection and analysis procedures. The section concludes with an examination of the relevant assumptions, limitations, delimitations, and ethical assurances associated with this project design.

## **Methodology and Design**

This section outlines the methodology employed to achieve the aims and objectives of the research study. It begins by briefly discussing the key research questions, along with the research aims and objectives, which serve as the foundation for developing the research strategy and design. The subsequent section delves into the research strategy and design, covering the research paradigm and the approach for addressing each research question and objective. Additionally, it reviews various potential research methods applicable to this study, providing a rationale for the selected research methods deemed most suitable for this project.

The project employs a qualitative, and exploratory case study design incorporating theoretical concepts from the Precautionary Principle and the most recent evidence concerning the maturity of QRM strategies in CDMOs. To assess Risk Management (QRM) maturity using qualitative research, this project will utilize methods like interviews and case studies to gather rich, contextual data about current practices, challenges, and perceptions of QRM within Startup X. The case study approach is grounded in the project's management problem and research purpose. Project Question 1 (PQ1) seeks to examine QRM maturity as it is currently practiced in Startup X rather than as an abstract concept, Project Question 2 (PQ2) implores the improvement of the current maturity and rigor of QRM strategies for start-up CDMO X, and Project Question 3 (PQ3) delves into understanding the barriers that Startup X faces in developing more rigorous QRM measures. Therefore, a qualitative exploratory case study is the most appropriate methodology for this study because it allows for an in-depth investigation of a complex phenomenon within its real-world context. The exploratory nature of the project design aligns with the fact that little to no existing research has specifically assessed QRM maturity in the

unique context of a CGT-focused CDMO startup. According to Frank T et al. (2008), Case studies are particularly well-suited to capturing context-dependent knowledge by exploring multiple perspectives from key stakeholders, as well as examining how organizational culture, regulatory compliance, and industry-specific challenges shape QRM strategies. Faulkner, S. (2021) suggests that this approach also enables the collection of rich qualitative data from multiple sources—including interviews, document reviews, and participant observation—enhancing the depth and credibility of the findings.

The Project Questions aim to study and evaluate existing risk maturity models in the pharmaceutical industry, as reviewed in the research literature, as well as alternative methods that might assist in performing an accurate diagnosis and comparison of risk management practices that will identify areas of strength in quality management practices and provide recommendations for impactful growth opportunities that could be implemented at Startup X. These research questions lean into the empirical part of the research where the risk maturity model proposed should be implemented in the sample and population in this project. The project questions will elucidate the characteristics of the sample as well as evaluate the reliability and consistency of the data collected. Specifically, leading to the main objective of the research, which is to analyze the maturity of Startup X's risk management practices that will enhance patient safety. Additionally, while answering this research question, it is imperative to demonstrate evidence that the proposed risk maturity model could be an instrument for the diagnosis of risk management practices. Moreover, these research questions will also assume the limitations of the risk maturity proposal and also discuss the possible agenda for the refinement of the QRM tools at Startups in future research.

## Methodology Approach

The methodology and methods that are considered appropriate for this project are presented here:

- **Qualitative:** A documentation review will be performed of risk theory, risk management, and Quality risk maturity models, as well as interviews with stakeholders. Additionally, pertinent documents and secondary information will be collected that could facilitate the study concerning the context in which QRM is performed at Startup X. Considering the operationalization of this research, the study's structure will be qualitative in nature and it shall be taken into account the shortage of research that is available in this field of QRM maturity, especially the lack of reasonable measurement theory for risk maturity models. In this sense, the principal objective of this research would be to conceptually evaluate an ICH based novel risk maturity model, reflecting on its theoretical assumptions as well as validating its propositions via the assessment of risk management practices in the pharmaceutical industry. As such, the efforts of this part of the study are intended to critically discuss and identify the gaps needed to adopt this type of methodology to risk management practices.

- **Exploratory:** Considering the Exploratory Design, a case study will be performed. The objective is to gain insight of maturity models at Startups in the pharmaceutical industry; with Startup X being the central point of focus.

Consequently, with a lack of theoretical foundation, many CDMOs do not follow the risk management cycle in order to structure the risk management practices prescribed in the case study. Hence the next step in this project will be to respond to the

difficulties in QRM application discovered by interviews conducted with current/past employees to clearly identify the theoretical reasoning behind QRM maturity which will allow for the proposal of a specialized model suitable for the characteristics consistent with an integrated approach of a more mature risk management in Quality.

To efficiently target PQ1, it is imperative to note that in the Pharmaceutical Industry, developers of cell and gene therapies (CGT) find it challenging to effectively translate a drug from a biological concept to a scalable and manufacturable treatment because there is a limited number of qualified personnel with both biological and process engineering know-how. Medvec et al. (2017). Other challenges include regulatory constraints and aggressive timelines from investors. As such, a CDMO can help an early-stage CGT developer understand the limitations of their source cells, by developing strategies around processing tissue, generating cell banks, or performing cell line engineering. Thus, engaging with a CDMO can also help navigate the evolving and nebulous regulatory landscape around CGT cell sources. National Academies of Sciences, Engineering, and Medicine. (2021). However, for startup CDMOs such as Startup X, effective risk management is crucial - risks are heightened in comparison to those of established firms, including unproven business models, Investigative New Drug Products (still in research mode), limited operational history, and dependence on a small manufacturing team. As such, PQ1 (Project Question 1) delves into recognizing risks early and crafting a strategy to tackle them so that startup CDMOs can improve their odds of overcoming obstacles. Furthermore, strong risk management demonstrates to investors that a startup CDMO understands potential challenges and is capable of managing them wisely risks. In

addition, CDMOs manage at a high level of risk – specifically financial risk from very expensive research programs with stakeholders, reputational risk from testing new drug products on humans, and constant regulatory compliance risk. Quon, S. (2025).

Risk Ranking is a critical aspect of Risk management. Ramnarine (2012). As such, Startup X’s QRM policy and related procedures should address risks to patient safety in the context of product quality and availability. Typically, risk ranking levels within a company’s QRM policy include ranking for GMP and regulatory compliance risks and patient safety risks based on product quality. O'Donnell (2012). The figures below provide an example of a risk ranking scale that incorporates considerations for both product quality and product availability in the ranking of patient safety risks.

Risk Ranking	Impact to Patients (Product Quality and/or Product Availability)	Impact to GMP Compliance
High	<ul style="list-style-type: none"> <li>Irreparable patient harm or death</li> <li>Shortage of a medically necessary (life supporting or life sustaining) product</li> </ul>	<ul style="list-style-type: none"> <li>Consent decree or warning letter</li> <li>Withdrawal of GMP certificate or manufacturing authorization</li> <li>Critical health authority observations or repeat inspection observations</li> <li>Systemic breakdown of GMP systems</li> <li>Recall</li> </ul>
Medium	<ul style="list-style-type: none"> <li>Reversible patient harm</li> <li>Shortage of product used for acute short-term or chronic long-term product indications</li> </ul>	<ul style="list-style-type: none"> <li>Major health authority observations</li> <li>High complaint rate</li> </ul>
Low	<ul style="list-style-type: none"> <li>No product or patient impact</li> <li>No shortage or multiple sources available for products that are not medically necessary</li> </ul>	<ul style="list-style-type: none"> <li>Minor observations</li> <li>Minor departures from GMPs</li> </ul>

**Figure 1. Risk Ranking and Impact on Patients and GMP Compliance**



**Figure 2 - Risk Ranking at the 5 Maturity Phases**

Moreover, PQ1 methodology focuses on assessing qualitative risk management principles through an exploratory case study of Waldron's 2017 QRM Doctoral thesis. It also evaluates supporting tools used by larger pharmaceutical manufacturers with advanced QRM maturity. Additionally, PQ1 compares these findings to Startup X to ascertain its current QRM maturity and identify improvement strategies for effective quality oversight in product development and manufacturing operations.

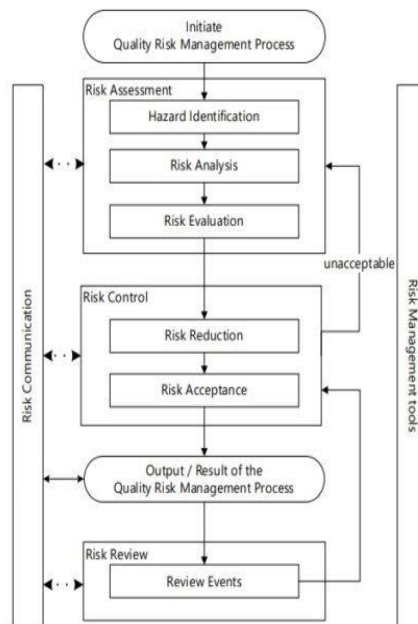
***How does Startup X evaluate the current QRM Maturity level?***

This involves evaluating how well Startup X identifies, assesses, and manages risks across its operations. First, the risk management framework at Startup X will be evaluated. A risk management framework is a set of policies, processes, tools, and roles that guide how the organization manages risks. It should align with strategic goals, organizational culture, and external standards. Ramnarine (2012). This includes examining the effectiveness of policies, procedures, and controls in place to mitigate risks and the organization's overall risk culture and awareness. A thorough assessment typically involves Data Collection Methods such as reviewing documentation, conducting interviews with key stakeholders, and analyzing past incidents or near-misses.

- **Interviews** – In-depth interviews with key stakeholders (Quality managers, Investor risk owners, Manufacturing process owners) elucidate an understanding of their perspectives on QRM practices, challenges, and opportunities for improvement at Startup X.
- **Document Review** – The examination of existing QRM documentation (policies, procedures, risk registers) is necessary to assess the current state of QRM practices.

By comparing the Startup X’s risk management practices against industry standards or best practices frameworks, such as ISO 31000, it becomes possible to determine its maturity level. This assessment helps identify strengths and weaknesses.

Moreover, Risk management practices also need to be evaluated. This includes various methods, such as surveys, further interviews, audits, or self-assessments, to collect data and feedback from different stakeholders, such as managers, employees, customers, or regulators. Focusing on key aspects of Startup X’s risk management practices, such as risk identification, assessment, control, monitoring, and reporting is paramount as it will facilitate integration of risk management with other functions, such as strategy, performance, and compliance.



**Figure 3 - The process of QRM**

## Data Analysis Techniques:

**Thematic Analysis** – Identify recurring themes and patterns in the data to understand the key aspects of QRM maturity.

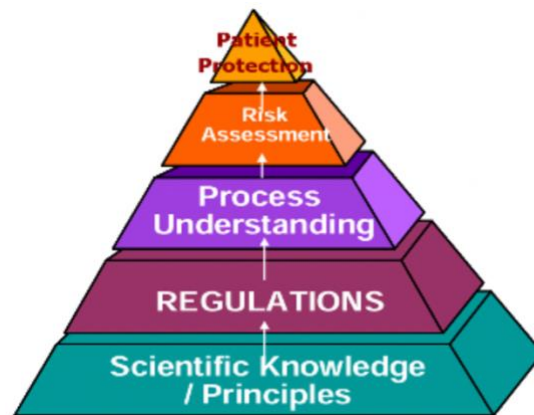
**Content Analysis** – Analyze the content of documents and transcripts to identify specific practices, challenges, and opportunities related to QRM.

**Framework Analysis** – Use a pre-defined framework or matrix to categorize and analyze the data, allowing for a systematic and structured approach.

**Narrative Analysis** – Explore the stories and experiences of participants to gain a deeper understanding of their perspectives on QRM.

## Risk Management Principle Assessment for Startup X

### *Quality Risk Evaluation for Startup X (ICH Expert Working Group (2005))*



**Figure 4 - Quality Risk Evaluation Pyramid**

- Compliance with applicable laws is an absolute requirement - Risk assessment is to be used to assess how to assure compliance and the resulting prioritization for action -- not for a decision regarding the need to fulfill applicable regulations or other legal requirements.
- Risk can only be effectively managed when it is identified, assessed, considered for further mitigation and communicated - This principle embodies the four general stages to an effective quality risk management process as defined by ICH Q9: 1) Risk Assessment (to include risk identification, analysis, and evaluation, 2) Risk Control (to include risk reduction and acceptance), 3) Risk Communication, and 4) Risk Review.
- All quality risk evaluations must be based on scientific and process-specific knowledge and ultimately linked primarily to the protection of the patient - Risk assessment is based on the strong understanding of the underlying science, applicable regulations and related processes involved with the risk under analysis. Collectively, these components are to be assessed first and foremost with regard to the potential impact to the patient.
- Risk assessment must take into account the probability of a negative event in combination with the severity of that event – This principle also serves a useful working definition for risk (i.e., risk represents the combination of the probability and severity of any given event).
- It is not necessary to always use a formal risk management process (e.g., standardized tools); the use of informal risk management processes (e.g., empirical assessment) is acceptable for areas of less complexity and lower potential risk, case in point Startup X GMP guidelines from FDA – In general, risk decisions are made by industry every day, in the course of regular business. The complexity of the events surrounding each decision and the potential risk involved are important inputs in determining the appropriate risk assessment methodology

and corresponding level of analysis required to ensure the appropriate risk decision is made. For the less complex and/or those decisions involving little risk, a qualitative analysis (e.g., decision tree) of the options may be all that is required. Generally, as the complexity and/or risk increases, so should the sophistication of the risk assessment tool used to facilitate the corresponding analysis.

- The level of documentation of the risk management process to render an appropriate risk assessment should be commensurate with the level of risk.

Startup X is determined to meet all stakeholder needs, from preclinical development all the way through to commercialization. Approaching stakeholder partnerships with a quality risk management (QRM) mindset is crucial for ensuring that Startup X can manufacture quality drug products and ensure patient safety. Faulkner (2021). As such, PQ2 leans into adopting mature quality management practices that will support a more reliable drug supply chain by reducing the occurrence of quality-related failures and improving the ability of establishments to maintain performance during expected and unexpected supply chain disruptions. Integrating business and manufacturing operations with quality practices and technological advancements can help achieve higher levels of maturity. Kolukisa (2020). This can optimize manufacturing process performance and product quality, enhance supply chain reliability, and foster proactive continual improvement. Richmond (2022). PQ2 concerns the need for improvement in the use of risk-based principles and tools when working to ensure that the manufacturing processes at Startups like Startup X that are used to produce drug products and their related equipment are appropriate. Manufacturing processes at CDMOs, even at Startups need to be validated (or proven) to demonstrate that they can produce a drug product of the required quality. Even the supplies and

items of equipment used in these drug manufacturing processes need to be qualified, in order to prove that they are fit for their intended use.

O'Donnell (2012) postulates that Quality risk management (QRM) tools can be used to support such qualification and validation activities, but their use should be science-based and subject to as little subjectivity and uncertainty as possible. When changes are proposed to manufacturing processes, equipment, or related activities, they also need careful evaluation to ensure that any risks present are managed effectively. Moreover, PQ2 aims to examine a practical approach to how QRM may be improved so that it better supports qualification, validation programs, and change control proposals in a more scientific way. This improved approach is based on the treatment of what are called good manufacturing process (GMP) controls during those QRM exercises. O'Donnell (2012). A GMP control can be considered to be any control that is put in place to assure product quality and regulatory compliance. This improved approach is also based on how the detectability of risks is assessed. This is important because when producing drug products, it is not always good practice to place a high reliance upon detection-type controls in the absence of an adequate level of assurance in the manufacturing process that leads to the finished drug product. Newton (2010).

***How will Startup X address the gaps and improve its risk management maturity level?***

It is imperative for Startup X to define improvement objectives, actions, responsibilities, timelines, and resources - By establishing how the organization will monitor and review progress and results, how it will align its improvement plan with stakeholder strategic plans, and ensure support and buy-in from leadership and staff. By defining the “when, where, and how” of risk management will startup X begin to see a measured growth of their risk management portfolio as

well as oversight to ensure the program is working as anticipated. Additionally, a defined role for QRM oversight sends a clear message that QRM is important to the organization.

How does QRM maturity then apply to Startup X? This applies to Drug Product development, the Manufacturing Process and subsequently the Distribution of the Drug Product to stakeholders:

- **Product Development:** (QRM) can help identify and mitigate risks associated with raw materials, manufacturing processes, and clinical trials during product development. By conducting risk assessments, Startup X can address potential hazards, evaluate the likelihood of adverse events, and implement preventive measures. A more mature QRM ensures that potential risks are proactively managed, leading to safer and more effective pharmaceutical products. Richmond (2022).

- **Manufacturing:** In this phase, QRM is crucial for ensuring product quality and preventing risks that could compromise patient safety. QRM can be used to assess and control risks related to equipment failure, operator error, contamination, and deviations from established procedures. By implementing risk control measures and continuous monitoring, Startup X can maintain consistent product quality and minimize the likelihood of defects.

- **Distribution:** QRM plays a significant role in the distribution of pharmaceutical drug products. Risks associated with transportation, storage, and handling can impact drug product quality and patient safety. QRM can be used to identify and assess risks in the distribution process, such as temperature control, product damage, and counterfeiting. Ramnarine (2012). By implementing risk control measures, such as proper handling and monitoring, Startup X can ensure that drug products reach patients in optimal condition.

Furthermore, it is imperative to measure risk management performance at Startup X. This includes defining and tracking key performance indicators (KPIs) and key risk indicators (KRIs) that reflect Startup X's risk appetite, tolerance, and exposure. Startup X should evaluate how its risk management practices contribute to its value creation, stakeholder satisfaction, and competitive advantage. Using KPI qualitative data to measure risk management performance will allow for a thorough comparison with targets and expectations.

In addition, Startup X should identify risk management gaps. Startup X's risk management maturity level involves a comprehensive evaluation of its current practices, processes, and culture related to risk management. To identify risk management gaps and assess maturity, consider the following steps:

- Framework Definition
- Gap Analysis
- Risk Identification
- Risk Assessment
- Risk Mitigation Strategies
- Risk Monitoring and Reporting
- Culture and Awareness
- Governance and Oversight

- Continuous Improvement
- Benchmarking and External Insights

Based on Startup X's evaluation and measurement, gaps should be identified between its current and desired risk management maturity level. Thus, the gaps should be prioritized according to their impact, urgency, and feasibility. Startup X should also consider the root causes of the gaps, such as lack of resources, skills, awareness, or commitment. These findings should all be documented and communicated to the relevant stakeholders and decision-makers so that a thorough risk management improvement plan can be drafted, as will be determined by PQ2

An effective risk management approach is a critical component of Startup X's resilience in the tough CDMO market as it can proactively anticipate potential risks and build robust contingency plans. These include but are not limited to:

- Identifying Key Risks: These risks can range from economic downturns, changes in the pharmaceutical industry regulatory landscape, supply chain disruptions, or natural disasters.
- Assessing Risk Mitigation Plans: Analyzing the effectiveness of risk mitigation plans determines how well it is prepared to handle potential risks. This involves evaluating the adequacy of stakeholder input, diversification strategies, supplier quality, and business continuity plans.
- Contingency Measures: Establishing contingency measures is crucial for a swift and effective response to unexpected events. This may involve creating a crisis management team, developing alternative supply chain networks, or implementing scenario planning techniques.

Let's consider the Drug product Manufacturing process at Startup X CDMO, operating in the highly volatile CGT industry. If in an instance, Startup X identifies supply chain disruption as a significant risk to its operations. To mitigate this risk, Startup X's manufacturing process has established alternative suppliers in different regions and has implemented real-time monitoring systems to identify potential disruptions early on. Now, comparing Startup X's Manufacturing's risk management strategies to its competitors in the CGT CDMO industry reveals that Startup X Manufacturing has taken proactive steps to establish resilience in the face of potential supply chain disruptions. This analysis provides valuable insights to Startup X Manufacturing, enabling them to further strengthen their risk management strategies and enhance their overall resilience.

Furthermore, in an ideal scenario, possessing all requisite documentation and having qualified personnel to execute a program would contribute to QRM's success at Startup X. Nevertheless, this does not represent the entire formula necessary for (QRM) maturity. Consideration for how risk management is perceived within Startup X lies in the initial stages of its implementation journey. According to the ICH Expert Working Group (2005), during the early phases of implementation, it is not unusual for QRM activities to be regarded as non-value-adding and merely a method to fulfill compliance requirements. Over time, with investment in the program, these perceptions are anticipated to evolve. On the other end of the spectrum, where the QRM program is optimized from the process and accountability perspective, QRM is likely to be viewed as a value add, and the organization realizes the benefits of QRM.

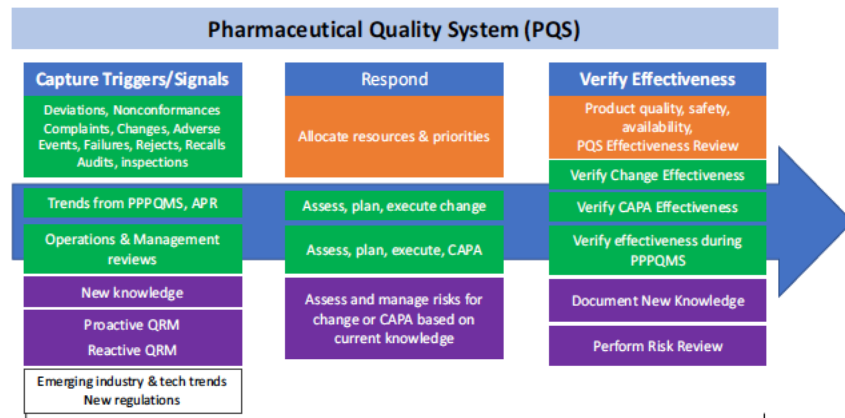
As such it is imperative to:

- Communicate the importance of risk assessments from a patient perspective.

- Let Startup X familiarize themselves with the fact that risk assessments take time because they are critical for demonstrating process understanding and knowledge management.
- Provide the support needed to ensure robust assessments are executed.
- Streamline processes to integrate proactive risk management activities into project plans so that failures are not assessed retrospectively.
- Evaluate quality systems to determine if there are activities in place that have been inadvertently duplicated through the risk management process.
- Identify ways to ensure that risk assessments are offering the utility intended. For example, using living risk assessments to inform change request(s) or for investigations.
- Determine if the organization's requirements for risk assessment or risk-based approaches are appropriately defined. Are there areas where risk assessments/risk-based approaches are required but a documented scientific rationale is sufficient?

Beyond compliance, Startup X should build a quality system that facilitates proactive quality management, enabling swift detection and mitigation of issues that might compromise drug product quality. This will in turn provide a framework for continuous improvement, allowing Startup X to enhance efficiency, reduce waste, and ultimately provide superior service to customers. An effective quality system instills a culture of quality within the organization. Employees become active participants in maintaining and improving quality, which can significantly enhance the overall performance of the organization. Low et al. (2014). Such a system is a key driver for building a robust brand reputation and fostering trust among patients, and stakeholders alike. This encompasses comprehensive GMP (Good Manufacturing) and GDP (Good Documentation) processes, procedures, and documentation addressing all aspects of quality control and quality assurance:

- Document Control: ensures all necessary documentation is accurate, updated, and readily accessible.
- Change Control: manages any alterations in internal procedures, systems, or processes in an organized manner.
- Deviation Management: addresses any departures from standard procedures.
- Supplier Qualification: effectively vetting suppliers to maintain the overall quality of medical supplies, instruments crucial to manufacturing process of drug products.



**Figure 5 - Pharmaceutical Quality System Chart**

*What are the primary barriers encountered by Startup X in improving the maturity of risk management strategies?*

PQ3 examines the challenges Startup X faces in developing stronger Quality Risk Management (QRM) measures. Startup X as a low level maturity CDMO may encounter challenges in maintaining an effective QRMS. This includes but is not limited to:

- Complexity of regulatory requirements
- Resistance to change within the organization
- Insufficient resources for quality initiatives

- Gaps in training and support for personnel
- Strategies to Overcome Challenges

Moreover, uncertainty is one of the elements that Startup X has examined through many decision-making processes as a Startup CDMO in the CGT Field. Sources of uncertainty include knowledge gaps in the pharmaceutical science and process understanding, sources of harm (e.g., sources of variability) and probably of detection of problems. As such, it is essential to assess the performance of systems, not people, to help drive fear of uncertainty out of the organizational culture. This means that when there are process failures or vulnerabilities exposed, they are evaluated as system failures rather than failures attributed to a specific risk owner or system owner. Also, it is important to note that previous models were developed primarily to characterize the business state of larger nonmedical companies. According to Richmond (2022), a maturity index designed specifically for startup companies in the CGT Pharmaceutical sector could help to identify areas in which targeted interventions could assist business development. Also, it is imperative to note that less mature establishments like Startup X struggles with data integration, which limits its ability to perform holistic reviews, gain a better understanding of overall business operations, and identify emerging hazards to quality. This limitation has severely limited Startup X's ability to identify opportunities for optimizing production operations and gaining more business processes from diverse clients. Having limited clients makes it more difficult to limit variability in QRM processes, as Startup X relishes in optimizing processes based on client needs, as opposed to having a more effective method or mechanism consistently in place to maximize the use of relevant data and sources of knowledge as CDMOs with more mature QRM processes do, which in turn enables them to optimize both production and business operations.

Furthermore, Startup X has also experienced a lack of progress in developing reliable ways to measure QRM in a process with respect to a) producing defective batches, b) running into quality issues that lead to delays in drug production, and c) serious GMP non-compliances. There are indications from regulatory inspection activities and quality defect investigations that current QRM activities at Startup X are still not sufficiently robust or effective, leading to highly subjective risk estimates and risk assessment outcomes, where the risks presented by hazards are not effectively managed and where the outcomes of risk assessment work often do not withstand regulatory scrutiny. For example, GMP deficiencies continue to occur in areas directly related to the management of risk (e.g., deviations, validation, change control, supplier oversight, product quality reviews). The following are some examples:

- Classifying recurring defects with a starting material as minor, despite the rejection of those lots due to critical defects
- Product Quality Reviews that conclude a process is in control despite high rates of batch failures, recurring deviations, and very low process capabilities
- Inappropriate actions taken after repeated line clearance failures rating suppliers as low risk despite recurring quality problems.

Additionally, Startup X has had further challenges in improving the maturity of its current QRMS by slapping the term “formal QRM” on everything without proper application or follow-through. Management here at Startup X will sometimes request a formal QRM process—i.e., using recognized tools like failure mode effects analysis (FMEA) be performed on issues ranging from the critical to the trivial. These are not tied to any formal Standard Operating Procedure and is simply at the rationale of the manager at the time. This broad misapplication of the QRM process has now caught the attention of good manufacturing practice (GMP) inspectors who now

see formal QRM reports addressing issues that in the past would have been decided simply on the basis of key GMP requirements that were well understood by management. Hence, using a risk-assessment tool to “justify” the release of a batch of product following a serious contamination incident, for instance, without reprocessing or reworking that batch, now appears to be occurring more frequently than in the past, with highly questionable batch release decisions in some cases.

In lower maturity CDMOs such as Startup X, consistency is key. Hence in these cases, it is often a greater show of QRM maturity to better focus efforts on simple root cause analysis and to take appropriate corrective and preventive actions (CAPAs) without overreliance on subjective risk assessments that could lead to the conclusion that the risk is low and that no actual CAPAs are needed. O'Donnell (2012). The maturity of an establishment is not dependent on factors like establishment size or age, and the types or number of products that are manufactured, tested, processed, packaged, labeled/re-labeled, or held. Rather, establishments with a highly mature quality culture use practices that invest time and resources commensurate with their financial resources to proactively improve their operations. Kolukısa (2020). Therefore, with a solid root cause analysis and a good understanding of the likely impact of a problem issue (on batch quality and to patients) in place, these approaches can often be more timely and effective than moving through all of the QRM phases, just to show maturity. Startup CDMOs like startup X with low level maturity sometimes fail to add value or clarity to a situation because an otherwise formal more mature QRM policy would only superficially address root cause analysis, resulting in ineffective risk-control actions. In addition, because risk assessments are often performed by busy people at startups with very little production time and pressing deadlines to manufacture a drug product for immediate release to a patient, the results are often not as supported by

scientific rigor as they should be. This can lead to high levels of subjectivity and uncertainty in outputs and conclusions, which further contribute to risk.

Consider, for example, a case involving a potential product contamination incident at Startup X's GMP Facility where drug products are manufactured. At the end of a drug product manufacturing process, the batch was found to have elements of fiber looking material involved in some of the final product. As a result, the product was given a "hold" status and placed into quarantine. In response to the problem, several actions were taken:

- A deviation was raised to investigate the issue, coupled with a formal risk assessment exercise (using FMEA) to decide whether to release the remaining batches.
- The risk assessment found that the fiber contaminants presented a low risk of batch contamination. This conclusion was used to justify the release of the quarantined batches to the patient, as only one drug product out of the 30 presented glass fiber. The fiber, after further testing, was also found to be residual elements of the starting material.

However, during a subsequent Regulatory audit, the inspector reviewed the QRM exercise, with the deviation notes. Significant problems were found with the aforementioned decision to release the batch to a patient. This cast considerable doubt on the validity of the QRM outcomes and the resulting batch release decisions. Because the empirical evidence gained from the deviation investigation was misinterpreted, scientifically unsound likelihood estimates were made that significantly affected the risk assessment outcomes. Furthermore, there was no documented clinical assessment of potential contamination and its risk to patients, nor a documented rationale as to why the batch was released to the patient in the first place. Therefore, having an advanced QRM policy that can determine when and how to implement a systematic

process for the assessment, control, communication, and review of risks to the quality and availability of the drug product across the product lifecycle is highly necessary at startup X. A proactive approach to increasing QRM maturity can minimize the occurrence of quality-related failures. Although Startup X has invested in some form of corrective actions in reaction to failures, it generally fails to devote resources to preventive actions to mitigate potential failure modes. More mature establishments utilize QRM principles and leverage knowledge throughout the lifecycle to make informed and timely decisions, and proactively review risks at an appropriate frequency to drive continual improvement and ensure availability of drug products. Newton (2010). Also, An advanced QRM policy would effectively uses quality principles (e.g., quality by design) and risk management approaches to ensure its continued suitability, capability, and reliability to minimize disruptions to drug production operations. This would consequently lead to greater production efficiencies and improved process performance and product quality, which can lead to reduced costs and a minimal occurrence of quality-related failures that can provoke drug delivery delays to patients. National Academies of Sciences, Engineering, and Medicine (2021).

Other barriers include the following:

- Regulatory barriers, including the challenges of fitting new technologies into existing regulatory frameworks, practices, and concepts; issues associated with inspecting facilities that have new technologies and with making changes after application approval; and the lack of international harmonization or regulatory convergence.

- Technical barriers, including inflexibility of manufacturing operations, thinking, and management and lack of process analytical technology that is needed to enable real-time quality assurance.
- Financial barriers, primarily the need for capital to implement a new manufacturing technology and the lack of a clear business case for making a change.
- Logistical challenges, including training requirements for industry, regulators, and investigators; competition for the small pool of needed new talent; issues surrounding intellectual property that make adoption of new manufacturing technology difficult; and lack of strategic partnering in the industry.

### **Risk Management Exploratory Design**

An exploratory case study design is particularly well-suited for examining the project questions within the context of the broader operational, organizational, regulatory, and competitive environments and constraints. QRM strategies and implementation do not occur in a vacuum, but are influenced by a variety of factors, including evolving regulatory requirements, technological advancements, and company-specific risk tolerance levels. Frank (2008). The case study design will allow the investigator to explore the complexities of QRM strategies in real time rather than relying on retrospective data that are void of context. The choice of a single-case study design and purposeful sampling of Startup X is justified by the study's exploratory nature and the complexity of QRM in CGT manufacturing.

In this case study, the objective is to analyze specific QRM projects examined by Waldron (2017) to understand how QRM processes were applied, what challenges were

encountered, and what lessons were learned as it applies to QRM maturity comparison to Startup X. Furthermore, an interview will be conducted with current/former Startup X employees 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 larger quality system. In this way, the interview will serve as a quantitative research method, enabling extensive analysis and trending of resultant data. This approach allows for an in-depth exploration of QRM maturity and factors influencing its robustness and consistency across client projects. In addition, the interview aims to assess the current existence of a QRM procedure or policy, compliance with ICH Q9, and audit status and results. The questions are designed for a specific focus on parameters such as people, process, and governance as it relates to Quality culture at Startup X. Moreover, the interview design should support the research objective and will be conducted via Zoom Workplace, where a transcript can be generated of the exchange.

Finally, the case study method allows for data triangulation which will strengthen the reliability of the project findings.

#### **Case Study Assessment Criteria on Waldron's 2017 paper**

- Case study can be compared to Startup X GMP System.
- Case study addresses a recognized area of general industry interest / application.
- Case study uses an approach that is consistent with ICH Q9 concepts and direction.
- Case study utilizes recognized quality risk management tools.
- Case study is appropriately simple and succinct to assure clear understanding.

- Case study provides opportunity for decreased and increased response actions.

A case study of Waldron's 2017 thesis represents risk assessment work which will be performed as part of QRM maturity assessment in the Pharmaceutical Industry. Waldron's (2017) thesis examines QRM's application in pharmaceutical companies and its role in managing patient risk. She characterizes a maturity state of QRM implementation that protects patients from risks linked to poor-quality medicines. Her research includes three phases: assessing patient protection since ICH Q9's publication; evaluating QRM maturity through its application, personnel attitudes and governance; and developing a mature QRM program and measurement tool to enhance QRM and patient safety. ICH Expert Working Group (2005). Additionally, Waldron's research utilized a mixed methods approach, incorporating research techniques such as literature review, philosophical dialogues, benchmarking surveys, semi-structured interviews, and pilot case studies. Waldron's (2017) findings indicate that overall patient protection has not significantly improved since QRM's introduction, and its maturity level in the pharmaceutical industry is still low. However, advancing towards the more mature QRM model proposed in the thesis could help companies implement QRM more effectively, resulting in improved risk management patient.

Moreover, the most commonly used basic risk management facilitation methods were flowcharts, check sheets, and risk ranking. Although Waldron sought to incorporate additional case studies that align with current good manufacturing practices, the outcomes and judgments from each risk assessment reflect the views of the authoring firm. Therefore, this inclusion should not be seen as establishing the individual quality-related conclusions. It also suggests that the example highlights a recognized area of quality focus and serves as a practical demonstration

of risk management utilized for effective analysis, problem-solving, and decision-making management. Waldron's study is organized in similar fashion according to the following general sequence:

- Introduction / Background - A brief summary is provided of the area of required risk assessment.
- Risk Question - The first step in the Quality Risk Management (QRM) process is to develop and agree upon the Risk Question. In the development of the Risk Question, it is important to first consider if there is any potential impact of the proposed actions to the patient. Evaluation of risks, when applicable, should ultimately be linked to the protection of the patient. Clearly defining the Risk Question facilitates selection of the appropriate tool, identifies relevant data, information and assumptions, assists in the identification of resources, responsibilities and accountabilities, and ensures that appropriate focus on the business objective is maintained.
- Risk Tool Selection - The selected Risk Assessment Method or Tool will be used to organize data, understand what steps can be taken to reduce or control risk and to help make appropriate decisions. In the selection of a Risk Assessment Method, it is recommended to evaluate the QRM process and to select the simplest tool available to support the process.
- Risk Assessment (Risk Identification and Risk Analysis and Evaluation) - The objective of Risk Identification is to develop a comprehensive analysis to include all applicable operations. At this stage of the QRM process, care should be taken to not exclude those operations which may be simply perceived as 'low risk', without fully evaluating the actual potential influences and associated potential risks involved. The Risk Analysis stage of the QRM process estimates the potential harm(s) associated with each potential risk. The analysis may be qualitative or quantitative in nature, or a combination of the two.

- Risk Control - During the Risk Control stage of the QRM process, a decision is made on which risks, if any, require mitigation and the necessary actions are taken in order to reduce or avoid all prioritized risks, as appropriate and practical.
- Risk Documentation and Communication - Communication of the QRM process should fully integrate key stakeholders into the QRM process. By ensuring that key stakeholders are engaged in both the data collection process for the Risk Assessment and the decision-making for Risk Control, the probability of organizational buy-in and support is maximized. The output of the QRM process and associated risk analysis justifying the approach, should be documented and endorsed by the site quality unit. Additionally, this information should be communicated to stakeholders for their information and to ensure their support.
- Risk Review - Appropriate systems should be in place to ensure that the output of the QRM process is periodically reviewed, as appropriate, to assess new information that may impact the original QRM decision. Examples of changes that may potentially impact risk of site operational systems include: changes to control systems, changes to equipment and processes, changes in suppliers/contractors, organizational restructuring, etc.

Through the combination of multiple data sources: interviews, documents, and participant observations, the findings will provide a comprehensive picture of QRM strategies and implementation in Startup X. Non-participant observations (e.g., QRM-related meetings or training sessions), the study can develop a comprehensive picture of QRM maturity. The integration of these multiple data sources is consistent with best practices in case study research and emphasizes the importance of understanding complex organizational phenomena from multiple viewpoints (Yin, 2018).

Subsequently, performing a case study on Waldron's 2017 research project provides empirical evidence that enables a comprehensive assessment and logical generalization, facilitating the broad application of QRM maturity models to Startup X's risk management design, along with strategies for data collection, sampling, and data analysis. It also addresses the ethical considerations essential to conducting the research. The development phases for maturity assessment models proposed by Waldron (2017) were used as a structure for this research project. Phase 1 comprises the determination of Waldron's scope, i.e. assessing patient safety in a pharmaceutical setting constituting specialized production of drug products for patient care; and thus evaluating QRM maturity through its application. Phase 2 includes the design of a conceptual maturity model substantially informed by existing frameworks for production planning and control, and incorporating the needs of the intended target group, as well as their personnel attitudes and governance towards QRM, i.e. managers, for production planning and strategies. Phase 3 comprises populating the model by deciding on the content and adjusting the conceptual model to the specific context. The identification of what was to be measured and how to measure it can be achieved through empirical data from Start up X.

### Alternative Methodologies

Several alternative methods were considered for this project but were ultimately deemed less appropriate for addressing the project questions. A quantitative cross-sectional survey design would identify correlations or patterns in organizational characteristics and QRM strategies. The focus of the quantitative research will primarily be on data analysis. Furthermore, explanatory sequential mixed methods commence with quantitative research, succeeded by qualitative techniques to enhance interpretation. This methodology is regarded as optimal for more

accurately assessing the current level of Quality Risk Management (QRM) adoption. Exploratory sequential mixed methods, conversely, initiate with qualitative approaches, followed subsequently by quantitative inquiries to assist in interpretation. These should include the following questions:

- Do the current Risk Assessment strategies potentially affect the potency of the drug product (i.e., the ability of the product to yield a given result for stakeholders)?
- Can the current Risk Assessment strategies potentially impact the sterility of the drug product?
- Can the current Risk Assessment strategies potentially impact the stability of the drug product?
- Can the current Risk Assessment strategies impact the performance of an analytical method?
- Can the current Risk Assessment strategies affect any of the above for another Drug products or manufacturing processes?

Although the design would allow for data collection among a larger sample population, the survey approach would lack the contextual depth needed to understand how organizational and environmental attributes influence QRM implementation. In addition, a survey design would not capture the subtle, situational factors that may result in barriers for more rigorous QRM measures. As a result of these constraints, a quantitative cross-sectional survey design was determined to be inappropriate for addressing the project questions. National Academies of Sciences, Engineering, and Medicine (2021).

In addition, a quasi-experimental design could be employed for this project. In this design, a controlled intervention, such as a mature, rigorous QRM measure, could be introduced in Startup X. Subsequent observations and surveys of staff and client perceptions and use of the new measure could be obtained in pre- and post-implementation design. Although the quasi-experimental design could provide more rigorous evidence of a causal relationship between organizational and staff adoption of mature QRM strategies in Startup X. The design would not allow for a deeper understanding of how multiple and various environmental pressures and competitive factors influence the decision on the appropriate level of QRM maturity and rigor of QRM measures. Based on this important limitation, the quasi-experimental design was determined to be inappropriate for addressing the project questions.

Finally, a phenomenology qualitative design could be used for this project. Phenomenology allows for the observation of individual lived experiences and the meanings participant apply to the experiences . A phenomenology approach would be appropriate for understanding the personal experiences of Startup X staff and clients regarding the implementation of QRM strategies. While these insights would be valuable, phenomenology would not provide a means of understanding the interaction of market, regulatory, and organizational context factors on QRM implementation. The focus on personal experiences does not provide the structured, contextually anchored analysis of organizational processes and multi-level factors that a case study offers. The phenomenology qualitative design was determined to be less effective than the case study method for addressing the project questions.

## Population and Sample

The population for this project consists of all CDMOs engaged in the production of cell and gene therapies (CGTs). These organizations play a pivotal role in the biopharmaceutical industry by facilitating the development and manufacturing of innovative therapies that are tailored to treat complex and often rare cancers and medical conditions. As the demand for CGTs continues to grow, the need for robust Quality Risk Management (QRM) strategies becomes increasingly critical to ensure product quality and patient safety. Despite this, the maturity of QRM strategies within CDMOs—particularly those that are newly established or in the early stages of development—remains largely unexplored.

Given the focus of this study on evaluating the maturity and robustness of QRM strategies, Startup X has been selected as the single case for in-depth examination. As a start-up CDMO specializing in CGTs, Startup X represents a purposeful sample within the broader population of CDMOs. The decision to focus on Startup X is driven by its relevance as a newly established organization navigating the challenges of implementing mature QRM strategies in a highly regulated and technically demanding environment. This case study aims to shed light on the unique circumstances and challenges faced by start-up CDMOs, providing valuable insights that can inform the development of more effective QRM practices across similar organizations.

Characterizing the maturity of a QRM program includes the assessment of multiple parameters including the people, risk culture, QRM initiation, risk assessment, risk control, risk review, risk communication, infrastructure, and governance. Richmond (2022). Two foundational elements are examined in this article: process and accountability. The process perspective evaluates the relative effectiveness of the QRM program strategy, documentation and the ability

of the organization to derive value from the program. The accountability perspective considers program ownership and organizational engagement. Process and accountability perspectives, in combination with understanding the cultural climate, can help us shape the Golden Mean or “just right” program size.

The sample for this case study will include key stakeholders within Startup X who are directly involved in the development, implementation, and oversight of QRM strategies. This includes suppliers and vendors of the materials to be used in the drug processing, as well as quality assurance managers, risk management personnel, project managers, and senior leadership. These stakeholders possess critical insights into the organization’s current QRM practices, the decision-making processes that influence risk management, and the barriers and facilitators to achieving higher maturity levels. By gathering perspectives from individuals across different levels of the organization, the study aims to construct a comprehensive understanding of how QRM strategies are perceived, developed, and operationalized within Startup X. Furthermore, the sample for this interview will include current/former employees of Startup X who have been directly and indirectly involved in the application of QRM methodology in their scope of work in the Quality Control Department; testing Drug products and Drug substances which would eventually be transported to hospitals and clinics and into patients.

### **Assumptions, Limitations, and Delimitations**

This section presents the assumptions, limitations, and delimitations associated with this project and that are common in an exploratory case study design. Identifying assumptions, limitations, and delimitations is important as they define the scope and boundaries of the case study and are critical for interpreting the findings responsibly and transparently (Need Citation).

## **Assumptions**

Assumptions are the elements of the study that are accepted as true or accurate without direct evidence or verification. Samaraweera (2017).

Assumptions in an exploratory case study design like this project include:

- **Truthfulness and Accuracy of Participant Responses:**

It is assumed that all participants involved in interviews or discussions will provide honest, accurate, and reflective responses regarding their knowledge and experiences with Quality Risk Management (QRM) practices at Startup X. Their insights are critical to capturing the depth and authenticity of the cases

- **Representativeness of the Selected Case:**

The case of Startup X is assumed to be representative of other early-stage or start-up CDMOs operating in the CGT space. While not intended to be generalizable in a statistical sense, the study assumes that findings from this case may offer transferable insights for similar organizations facing comparable challenges.

Moreover, Startup X is assumed to be representative of an an Early-Stage Focus Startup:

Many pharmaceutical startups focus on the early stages of drug discovery and development, identifying potential new drug targets and developing innovative therapies – as is the case of Startup X with a niche drug product manufacturing for Oncology late stage patients.

- **Availability and Access to Data:**

It is assumed that the researcher will have adequate access to relevant internal documents, QRM frameworks, and key stakeholders. This includes assumptions that participants are willing to engage and that documentation is sufficiently detailed and current to support analysis.

- **Organizational Stability During Data Collection:**

The study assumes relative organizational stability during the period of data collection—i.e., no major structural changes, regulatory crises, or leadership turnover that would significantly alter the QRM practices under investigation.

**Limitations**

Limitations are the potential weaknesses or constraints in the study that are beyond the researcher's control. Ingram (2023).

**Limitations in a study like this include:** We state that current risk maturity models at Startup X do not meet the requirements and specifications of larger biopharmaceutical companies. As discussed by MacGillivray (2020), most of the QRM models examined, claim to assist organizations in implementing a formal approach to risk management or to improve their existing approach. Most of the time these models would be intended as diagnostic tools instead of prescriptive instruments for implementation MacGillivray, (2020). Limitations also include Resource constraints – difficulty in collecting and analyzing data. Although the case study considers the improvement of risk maturity models in Waldron's (2017) research, there is a lack of research specifically carried out for these larger organizations in the CGT Biopharmaceutical industry.

**Limited Generalizability:**

As a single-case exploratory study, the findings are context-specific and may not be broadly generalizable to all CDMOs. While the insights may inform practices in similar settings, they are not statistically representative of the entire industry. Furthermore, most of the aforementioned methods could be sufficient for establishing a broad course for organizations willing to introduce themselves to the discipline of risk management. They have been successful in adapting maturity models from the original perspective of QRM, towards risk management practices for the healthcare sector and industry where they have been applied. Nevertheless, some specific criticisms may be considered. Additionally, in the review of the general maturity models studied in this research paper, there lies in general, a lack of theoretical and empirical support for the construction of QRM that are only based on the experience of experts and practitioners. Especially recognizable is the nonexistence of a theoretical fundament that could explain the reasoning behind this sequence of steps that a startup organization like Startup X would have to follow. It would necessitate becoming aware of a new practice and learning about risk management through the guiding of this special framework until achieving a master performance.

#### **Reliance on Subjective Data:**

The study relies heavily on qualitative data, including interviews and document reviews, which are inherently subjective. Participant responses may be influenced by recall bias, organizational loyalty, or professional agendas, potentially affecting the objectivity of findings.

#### **Potential Researcher Bias:**

Given that the researcher is an employee of Startup X and directly involved in QRM processes, there is a potential for bias in data interpretation and analysis. Although strategies will be implemented to mitigate this (e.g., external review of coding), the researcher's positionality may still influence findings.

### **Access and Confidentiality Constraints:**

Some QRM documentation or discussions related to proprietary processes may be restricted or confidential, limiting the scope of data available for analysis and potentially resulting in incomplete understanding of the QRM system's full implementation.

### **Delimitations**

Delimitations are potential weaknesses of the study that are within the control of the researcher. The potential weaknesses are inherent based on decisions associated with the study's focus, methodology, sample size. In crafting a feasible dissertation project, the researcher must effectively define the boundaries of the project which have consequences in regards to generalizability of the findings (Need Citation).

### **Delimitations in a study like this include:**

- Focus on a Single Organization (Startup X):

This study deliberately focuses on one start-up CDMO to allow for a deep, contextualized analysis of QRM maturity. This decision excludes comparative insights from other CDMOs, including larger, more established organizations.

- Emphasis on Cell and Gene Therapy Manufacturing:

The study is confined to QRM practices related to CGT production. It does not examine risk management in traditional small-molecule or biologics manufacturing, as the regulatory, technical, and operational contexts differ significantly.

- Use of Waldon's Maturity Model as the Analytical Framework:

The study uses Waldon's (2017) model to assess QRM maturity. Other models or frameworks for assessing quality maturity are not used, as Waldon's model is well-aligned with the study's purpose of evaluating both process rigor and patient safety orientation.

- Exclusion of Quantitative Risk Metrics:

The project is limited to qualitative analysis and does not incorporate quantitative data such as deviation rates, CAPA (Corrective and Preventive Actions) metrics, or audit scores. The focus is on perceptions, processes, and qualitative indicators of maturity, not numerical performance indicators

### **Ethical Assurances**

This applied dissertation project will be reviewed and approved by the National University Institutional Review Board (IRB) prior to the initiation of any data collection activities. The IRB review ensures that the study complies with all ethical standards for research involving human participants, including issues related to informed consent, confidentiality, privacy, and protection from harm. No interviews, document reviews, or observations will be conducted until formal IRB approval is granted. Startup X, the organization participating in the study, will also provide site authorization, confirming organizational consent to participate in the research and allowing access to relevant personnel and internal documents.

Confidentiality and data security will be strictly maintained throughout the project. All participants will receive an informed consent form that outlines the purpose of the study, their voluntary participation, the option to withdraw at any time, and how their data will be protected. Pseudonyms will be used for the organization (Startup X) and for all individuals participating in interviews to ensure anonymity. Any identifiable information will be removed from transcripts and documentation. Data will be securely stored in password-protected files on encrypted devices and backed up in a secure cloud storage service approved for research use. Access to the data will be limited to the researcher and, if necessary, the IRB. Data will be retained for three years after the study concludes and then permanently deleted.

### **Role of the Scholar-Practitioner**

The scholar-practitioner conducting this research is also an employee of Startup X and is directly involved in the development and implementation of Quality Risk Management (QRM) strategies for client projects. This dual role presents a potential risk of bias or perceived conflict of interest. This project includes several strategies to mitigate potential researcher bias. First, interview transcripts will be reviewed by participants to ensure accuracy and validation of responses. Second, the researcher will maintain a journal to document personal thoughts, assumptions and reflections during the research process to help identify potential bias. Third, the researcher will hold regular discussions and debriefings with her dissertation advisory committee to obtain external perspectives, challenge assumptions, and ensure a balanced analysis. Finally, the researcher will be transparent regarding the possibility of bias by acknowledging their dual role in the project.

## Summary

By focusing on Startup X, the case study captures the nuances and contextual factors that may be overlooked in broader, multi-case analyses. The case study highlights various applications of structured risk management analysis that indicate the applicable QRM maturity at that stage, which will ultimately support effective decision-making. It emphasizes the need to choose the right risk methodology based on maturity, specific requirements, and risk complexity. Additionally, predefining risk categories is crucial to minimize the impact of assessment results on response actions. Quality risk maturity Management (QRMM) is now deemed to be a regulatory expectation, and it makes good business sense. Richmond (2022). The goal of the risk assessment is to increase understanding of the drug manufacturing process at Start-up X and deliver safe and effective drug products to the patients. Risk analysis and management is an acceptable and effective way to minimize patient risk and determine the appropriate level of controls in manufacturing. While understanding the elements of the maturity of the QRM program is important, knowing how to apply them in the manufacturing environment at Startup X is essential for effective process performance and control. As such, this project aims to elucidate the application of QRM in pharmaceutical manufacturing to illustrate how QRM can help the reader achieve that objective. QRM tools can be used effectively to identify the risks and develop strategy to minimize or control them. Risks are associated throughout the biopharmaceutical manufacturing process—from raw material supply through manufacturing and filling operations to final distribution via a controlled cold chain process. Assessing relevant attributes and risks for biotechnology-derived products is more complicated and challenging for complex pharmaceuticals. Phuong (2019). Therefore this paper discusses key risk factors in biopharmaceutical manufacturing.

Finally, after assessing and prioritizing risks, clear risk-mitigating actions should be defined, communicated, implemented, and monitored for effectiveness. Furthermore, insights from Startup X can serve as a valuable reference point for other start-up CDMOs seeking to enhance their QRM strategies and achieve a balance between client requirements and patient safety considerations. Moreover, the population for this project consists of all CDMOs engaged in the production of cell and gene therapies (CGTs). These organizations play a pivotal role in the biopharmaceutical industry by facilitating the development and manufacturing of innovative therapies that are tailored to treat complex and often rare medical conditions. Medvec (2017). As the demand for CGTs continues to grow, the need for robust Quality Risk Management (QRM) strategies becomes increasingly critical to ensure product quality and patient safety. Despite this, the maturity of QRM strategies within CDMOs—particularly those that are newly established or in the early stages of development—remains largely unexplored .

Given the focus of this study on evaluating the maturity and robustness of QRM strategies, Startup X has been selected as the single case for in-depth examination. As a start-up CDMO specializing in CGTs, Startup X represents a purposeful sample within the broader population of CDMOs. The decision to focus on Startup X is driven by its relevance as a newly established organization navigating the challenges of implementing mature QRM strategies in a highly regulated and technically demanding environment. This case study aims to shed light on the unique circumstances and challenges faced by start-up CDMOs, providing valuable insights that can inform the development of more effective QRM practices across similar organizations.

The sample for this case study will include key stakeholders within Startup X who are directly involved in the development, implementation, and oversight of QRM strategies. This

includes quality assurance managers, risk management personnel, project managers, and senior leadership. These stakeholders possess critical insights into the organization's current QRM practices, the decision-making processes that influence risk management, and the barriers and facilitators to achieving higher maturity levels. By gathering perspectives from individuals across different levels of the organization, the study aims to construct a comprehensive understanding of how QRM strategies are perceived, developed, and operationalized within Startup X.

### **Section 3: Findings, Implications, and Recommendations**

This section examines the findings concerning the dissertation's problem, purpose, and questions, with a particular focus on the maturity of Startup X's QRM system. The evidence indicates that Startup X is in an emergent to early development stage (Waldron, 2017), facing challenges such as unclear escalation roles, inactive risk registers, governance problems during leadership transitions, irregular audits, and resource constraints. These issues suggest a reactive, compliance-driven risk culture instead of a proactive one that prioritizes learning, governance, and safety.

The connection to the pharmaceutical market further contextualizes these findings, as these organizational challenges align closely with patterns documented in the broader literature on early-stage CDMOs. Research shows new or growing CDMOs often face volatile documentation, weak governance, limited training, and inconsistent leadership, especially under market pressures (ISPE, 2015; FDA, 2021). These issues hinder both internal efficiency and external credibility, making it harder for CDMOs to meet clients' demand for demonstrated QRM maturity. Such gaps pose compliance risks and threaten long-term competitiveness by eroding client trust and strategic stability.

This section serves two main purposes. first, it assesses Startup X's maturity in Waldron's framework, connecting organizational weaknesses to academic and regulatory challenges. Next, it prepares recommendations and an action plan. It details Startup X's maturity profile through participant accounts and documentation, ending with findings on governance, cross-learning, culture, and patient outcomes. By positioning Startup X within theoretical and industry contexts, this section provides a diagnostic perspective and paves the way for practical,

evidence-based strategies to transition the organization from reactive practices to a structured, sustainable QRM maturity level.

## **Findings by Project Question(s)**

### **Project PQ1 Analysis**

#### **PQ1: How mature are Startup X's QRM strategies, and how effectively are they implemented across the organization?**

Startup Contract Development and Manufacturing Organizations (CDMOs) struggle to balance patient safety and product quality with the need to meet fast-paced client demands and manage limited resources. In early-stage settings, Quality Risk Management (QRM) systems often are underdeveloped, resulting in inconsistent use, insufficient preventive measures, and weak alignment with organizational culture and leadership. For Startup X, anecdotal evidence and previous observations indicated that QRM practices were applied unevenly, heavily influenced by client requests, and hampered by communication, training, and governance gaps.

Startup X's QRM is **documented but inconsistently implemented**. Across three QC/QRM-adjacent participants, common patterns emerged: underdeveloped governance, leadership turnover, resource constraints (tools, LIMS, calibration), poor cross-site and cross-department communication, a reactive 'firefighting' culture, and repeated pressure to prioritize client demands over internal QA/QRM principles. These patterns align Startup X with **Level 2 (Managed)** on Waldron's (2017) maturity continuum: some processes exist but are not embedded or consistently applied. The report below lays out the detailed thematic analysis, interprets findings against the literature/Waldron's model, evaluates outcomes, and gives an action plan to move toward Level 3 (Defined) then Level 4 (Managed + Predictive).

The purpose of this qualitative case study was to evaluate the maturity of QRM strategies at Startup X using Waldron's (2017) QRM Maturity Model. The research aimed to:

1. Assess the current state of QRM processes, governance, and culture at Startup X.
2. Identify strengths, gaps, and improvement opportunities in QRM implementation.
3. Explore alignment between QRM practices and patient safety, product quality, and stakeholder needs.
4. Generate recommendations for advancing QRM maturity to better meet regulatory expectations and competitive market demands

### **Raw Preliminary Findings**

- QRM existence but poor enactment — SOPs, risk logs, and QRM language exist but are often not followed in practice.
- Reactive rather than preventive culture — repeatedly described “wait until it happens” approach; participants recommended a `preventive focus.
- Leadership instability undermines governance — motivated QRM leaders arrived briefly but turnover left initiatives incomplete (risk register reviews started then faded).
- Communication and people issues are central barriers — cross-site handoffs, document loss, siloed meetings, and “don’t escalate” cultural norms.
- Resource & systems gaps — lack of LIMS/QMS, missing licenses, calibration delays, fragmented document control.
- Client-pressure conflicts with GMP/QRM — participants report being pushed to follow client preferences at times inconsistent with best practice.

### **Overview of QRM Maturity at Startup X**

The findings from participants illustrate a fragmented and fragile maturity level in Quality Risk Management (QRM) at Startup X. Although strategies are documented and sometimes superficially acknowledged, they are not consistently implemented throughout the organization. This indicates that Startup X most closely aligns with Level 2 – Managed within

Waldron's (2017) QRM Maturity Model. At this level, processes may be documented but are not systematically applied, and the organizational culture remains reactive rather than proactive.

(Waldron, 2017; ICH Q9(R1), 2023)

### **QRM Awareness**

Awareness of QRM principles varied among participants. The interviews confirmed this fragmented awareness. For example, one person admitted that “QRM was never even mentioned,” while another only learned about the concept after joining Startup X. These reflections highlight that awareness was left to chance and individual exposure rather than being a deliberate organizational strategy (Waldron, 2017). Without embedding awareness at a cultural level, QRM cannot function effectively.

This variation indicates Level 1–2 maturity, where knowledge is scattered and not widely adopted across functions (Waldron, 2017). QRM terminology appeared only sporadically across SOPs and policies, suggesting that awareness was not fully embedded into the company's governance systems. References to QRM principles were vague and inconsistent, with no evidence of structured reinforcement mechanisms to ensure all staff understood risk-based processes. Without a shared understanding of QRM's role in protecting processes and patients, its implementation stays superficial and unsustainable. As a result, weak awareness seriously hinders Startup X's ability to integrate QRM strategies into everyday practice.

“QRM was never even mentioned.” (Participant #2)

### **Documentation Gaps**

Throughout interviews, participants identified significant challenges with SOPs, such as conflicting versions, offline copies, and missing escalation pathways. Documentation is a key part of QRM maturity; without accurate, consistent, and accessible governance documents, risk-based decision-making cannot be consistent. Startup X's current status corresponds to Level 2 of Waldron's model, where processes are in place in theory but are incomplete or applied inconsistently (FDA, 2006; Waldron, 2017). Moreover, contradictions and version conflicts, as well as missing escalation pathways, created ambiguity. As one participant put it, "Even when we had the SOPs, no one was sure which version to follow" (Participant #3). This inconsistency illustrates a governance system in its infancy; characteristic of Level 2 maturity. These documentation issues not only hinder effective implementation but also create compliance vulnerabilities. The interviews reinforced this weakness, while staff noted that even with SOP documents present, they were not consistently applied (Waldron, 2017).

"Even when we had the SOPs, no one was sure which version to follow" (Participant #3)

### **Training Effectiveness**

Training emerged as another area of weakness. Participants described QRM training as "minimal," "late," or "not enough," with some recalling only a single unofficial session. Structured, comprehensive training is essential to embedding QRM culture, yet Startup X relies on ad hoc approaches that leave employees underprepared. This finding situates the organization within Level 1–2 maturity, where training is reactive and unstructured (ISPE, 2015; Waldron, 2017). Without deliberate investment in formalized training curricula, Startup X cannot achieve

sustainable cultural change or consistent implementation. Weak training undermines both awareness and practice, ensuring that documented strategies remain aspirational rather than operationalized.

“I probably had one unofficial training session... it wasn’t enough.” (Participant #2)

### **Process Implementation**

Perhaps the most noticeable gap is the disconnect between policy and practice. Although risk registers and QRM-approved SOPs exist, participants admitted these tools are often ignored: “Sometimes we just skip the risk register altogether because it slows things down” (Participant # 1). This “knowing–doing gap” highlights a lack of operational discipline and confirms that Startup X remains at Level 1–2 maturity culture (Waldron, 2017). This disconnect between theory and practice illustrates Startup X’s immaturity and reactive culture.

“Sometimes we just skip the risk register altogether because it slows things down” (Participant # 1).

### **Leadership Commitment**

Leadership commitment to QRM was described as inconsistent and diluted by turnover. While one participant noted that a director actively requested risk logs, others observed leaders cutting corners or deprioritizing QRM under operational pressures. Leadership is a pivotal determinant of QRM maturity; fragmented sponsorship leaves staff with mixed signals and perpetuates a reactive culture. On Waldron’s scale, this situates Startup X at Level 2, where leadership awareness exists but is neither stable nor fully embedded (Waldron, 2017; FDA,

2006). Sustained executive sponsorship will be essential for advancement to higher maturity levels. Until QRM principles are consistently applied in daily operations, the organization's maturity will stay limited. Inconsistent executive sponsorship keeps QRM maturity at a low level.

“Our director actually asks to see our risk logs.” (Participant #3)

“Leaders cut corners.” (Participant #1)

### **Patient Safety Impact**

Importantly, the immaturity of Startup X’s QRM strategies has already manifested in risks to product quality and patient safety. One participant disclosed that “inconsistent risk review has put a couple of batches at risk.” This is highly significant, as QRM maturity is not merely a compliance exercise but ultimately a safeguard for patients. Startup X’s current posture corresponds to Level 1–2 maturity, characterized by a reactive response to risks rather than a proactive prevention mindset (ICH Q9(R1), 2023). This deficiency underscores the urgency of strengthening QRM infrastructure and culture. Immaturity in QRM translated into product-level concerns with potential consequences for patients. This is a critical red flag in terms of both compliance and safety outcomes.

“Inconsistent risk review has put a couple of batches at risk.” (Participant #2)

## **Governance and Resource Gaps**

Finally, Startup X lacks a formal governance structure for QRM, with no clear oversight roles or escalation mechanisms. Governance is a central pillar of Waldron’s higher maturity levels, and its absence cements the organization at the lower end of the scale. Additionally, participants cited resource constraints — including insufficient staffing, tools, and time — which hinder the ability to institutionalize QRM. Both issues reinforce Startup X’s position at Level 2, where organizations may recognize the value of QRM but lack the structure and resourcing to implement it effectively (ISPE, 2015; Waldron, 2017). These constraints hinder QRM from moving beyond a compliance burden into a strategic enabler (Waldron, 2017).

“We don’t really have a governance structure like the model outlines.” (Participant #1)

Table X below presents a summary of the findings by QRM maturity domain. Beyond Waldron’s (2017) model, the broader QRM literature highlights the importance of integrating risk-based thinking into organizational culture and practices. The ICH Q9(R1) (2023) guideline stresses that QRM is an ongoing, lifecycle-focused process spanning development, manufacturing, and post-market phases

Startup X’s QRM maturity is low, fragile, and inconsistent. While there are isolated examples of leadership engagement and emerging awareness, these are hampered by systemic weaknesses in documentation, training, governance, and process implementation. Startup X’s QRM culture remains reactive, siloed, and compliance-driven, rather than focused on prevention and patient-centeredness.

On Waldron's maturity continuum, Startup X is positioned between Level 1 (Initial/Ad hoc) and Level 2 (Managed), showing occasional indications of more advanced practices that are not yet fully integrated. Until governance structures are formalized, leadership commitment is enhanced, and investments are made in training and resources, Startup X will find it difficult to progress toward the higher, proactive, patient-centric maturity levels (Levels 3–5). Most importantly, the analysis emphasizes that current maturity gaps create tangible risks to patient safety, highlighting the urgent need for organizational change. PQ1 thus not only exposes the immaturity of Startup X's QRM strategies but also demonstrates the direct consequences of this weakness, reinforcing the necessity for targeted improvements in governance, culture, and systems if the organization aims to advance along Waldron's maturity model.

**Table 2. Summary of QRM Maturity Level Findings by Theme**

<b>Theme</b>	<b>Document Evidence</b>	<b>Interview Evidence</b>
<b>QRM Awareness</b>	References to QRM sporadic in SOPs, not reinforced (Waldron, 2017).	Awareness fragmented; staff only learned QRM informally.
<b>Documentation Gaps</b>	Conflicting SOP versions; missing escalation pathways (FDA, 2006).	SOPs hard to follow; contradictions and gaps noted (Waldron, 2017).
<b>Training Effectiveness</b>	Minimal training documentation; no formal curriculum (ISPE, 2015).	Training ad hoc, insufficient, poorly timed (Waldron, 2017).
<b>Process Implementation</b>	Risk registers and SOPs existed but not utilized (Waldron, 2017).	Staff admitted processes bypassed; corner-cutting common.
<b>Leadership Commitment</b>	Leadership roles vague in documents (FDA, 2006).	Mixed behaviors: some leaders supportive, others cut corners (Waldron, 2017).
<b>Patient Safety Impact</b>	Few links between QRM and safety in documents (ICH Q9(R1), 2023).	Risks noted at product level: batches put at risk (Waldron, 2017).
<b>Governance &amp; Resources</b>	No governance structure or escalation mechanisms (ISPE, 2015).	Staff shortages and leadership turnover hindered QRM (Waldron, 2017).

## **Project PQ2 Analysis**

***PQ2: What evidence-based improvements can be recommended to improve the maturity of Startup X's current QRM program?***

### **Overview of the Problem and Purpose as it relates to QRM Maturity at Startup X**

Startup X, a rapidly growing CDMO, is at a critical stage where the maturity of its Quality Risk Management (QRM) strategies directly influences its regulatory compliance,

operational consistency, and patient safety. Although QRM frameworks, such as ICH Q9 and Waldron's (2017) maturity model, provide clear pathways for integrating risk management principles into organizational practices, evidence from the participant interviews suggests that Startup X has not yet fully institutionalized QRM to create a strong, sustainable system. The purpose of this dissertation is to examine the maturity of Startup X's QRM strategies, identify gaps in practice, and provide evidence-based recommendations for strengthening its QRM program. Project Question 2 specifically addresses the need for actionable improvements: "What evidence-based improvements can be recommended to improve the maturity of Startup X's current QRM program?"

## **Findings**

### ***Documentation Gaps and Governance***

The interviews consistently revealed that documentation practices were fragmented, with multiple offline versions of SOPs and unclear escalation pathways. These documentation weaknesses represent a hallmark of organizations functioning at Waldron's Level 2 (Developing), where processes exist but lack consistency or clarity. To advance maturity, Startup X must adopt stronger document version control systems, embed escalation responsibilities directly into SOPs, and establish periodic audits. Such changes would not only improve governance structures but also elevate Startup X to Level 3, where processes are standardized and more reliable.

### ***Training Effectiveness and Workforce Capability***

Training emerged as another major gap. Staff described their QRM training as minimal, one-off, and insufficient for application in practice. This reflects a Level 1–2 maturity posture, where training is ad hoc rather than institutionalized. To address this, Startup X should

implement a structured QRM training curriculum consisting of onboarding, scenario-based exercises, and regular refreshers. By adopting training that transfers knowledge into applied skill, the organization would progress toward Level 3–4, where training becomes an enabler of consistent QRM implementation across the workforce.

### ***Process Implementation and Operational Consistency***

The implementation of QRM processes was notably inconsistent. Although risk registers and approved SOPs existed, they were rarely used in practice. This gap between policy and execution highlights a common barrier at Level 2 maturity. Embedding QRM tools directly into operational workflows—such as requiring risk reviews at batch kickoff meetings, change control boards, and tech-transfer events—would help bridge this gap. With these practices in place, Startup X would achieve greater alignment with Level 3, where QRM processes are actively applied and verified across operations.

### ***Cultural Resistance and Preventive Mindset***

The cultural orientation toward QRM was described as reactive, with participants stating, “we’ll deal with it when it happens,” and admitting to cutting corners to meet deadlines. This is consistent with Waldron’s Level 2, where risk is viewed as a compliance requirement rather than a proactive organizational value. To transform this culture, Startup X should launch a preventive initiative, encouraging staff to anticipate risks rather than defer them. Campaigns that reward preventive actions and normalize risk communication would help shift the organization closer to Level 4 (Managed), where a culture of prevention is embedded.

### ***Leadership Commitment and Stability***

Leadership engagement was inconsistent, with some directors taking interest in QRM logs while others deprioritized QRM to focus on immediate deliverables. Leadership turnover

further eroded momentum. These characteristics are typical of Level 2 maturity, where leadership involvement is episodic rather than sustained. Formalizing a QRM Governance Charter that names risk owners, defines escalation pathways, and establishes a monthly leadership risk review cadence would stabilize governance. By doing so, Startup X could progress toward Level 4 maturity, where leadership consistently models and enforces QRM principles.

### ***Patient Safety Integration***

Perhaps the most concerning finding was the direct impact on patient safety. Participants noted that inconsistent risk review had placed product batches and dosing accuracy at risk. This reactive approach situates Startup X at Level 1–2 maturity, where safety outcomes are jeopardized by the absence of systematic QRM integration. To improve, Startup X must embed patient safety considerations into every risk review, ensuring that potential patient outcomes are explicitly evaluated. Such integration represents a higher level of maturity (Level 4–5), where QRM becomes inseparable from patient-centric decision-making.

### ***Governance Structures and Waldron Gaps***

A clear gap emerged between Startup X's current state and the governance expectations outlined in Waldron's model. Participants openly acknowledged that no formal governance structures existed for QRM oversight. Without governance, the organization cannot rise above Level 2 maturity. Establishing a governance committee, assigning formal risk ownership roles, and conducting annual maturity self-assessments would close this structural gap and align Startup X with Levels 3–4, where governance provides accountability and continuity.

***Resource Constraints and Infrastructure Needs***

Finally, participants highlighted resource shortages that hindered QRM implementation, including limited software licenses, staffing constraints, and delayed access to tools. These barriers are symptomatic of Level 2 organizations that lack infrastructure to sustain consistent practices. By investing in adequate resources and removing operational bottlenecks, Startup X could provide the foundation required to support Level 3 maturity.

**Table 3: Strategic Roadmap - Linking Improvements to Waldron’s Model**

<b>Theme</b>	<b>Recommended Improvement</b>	<b>Current Level</b>	<b>Target Level</b>	<b>Outcome Alignment</b>
Documentation Gaps	SOP version control, escalation RACI, audits	2	3	Governance & clarity
Training Effectiveness	Tiered curriculum & refreshers	1–2	3–4	Workforce capability
Process Implementation	Risk registers, huddles, evidence trails	2	3	Operational consistency
Cultural Resistance	Prevent Before Produce initiative	2	4	Culture of prevention
Leadership Commitment	QRM Governance Charter, KPIs	2	4	Sustained sponsorship
Patient Safety Impact	Safety checklists in reviews	1–2	4–5	Patient-centered QRM
Waldron Model Gap	Governance committee & self-assessments	2	3–4	Structural alignment
Barrier Resource Limit	Tools, staffing, IT access	2	3	Infrastructure readiness

**Project Question 3 Analysis**

***Project Question #3: “What are the primary barriers encountered by Startup X in improving the maturity of risk management strategies?”***

**Overview of the Problem and Purpose as it relates to QRM Maturity at Startup X**

Startup X operates in a complex regulatory and market environment where the maturity of its Quality Risk Management (QRM) strategies is critical for compliance, patient safety, and

competitiveness. While Project Questions 1 and 2 explored the current maturity state and evidence-based improvements, Project Question 3 focuses specifically on the primary barriers that hinder the organization’s ability to advance its QRM maturity. Understanding these barriers is crucial because the thematic analysis uncovers both fundamental causes and subsequent effects, which together explain why Startup X has difficulty moving beyond a reactive QRM stance.

The purpose of this section is to analyze participant insights on barriers, interpret them in light of Waldron’s (2017) QRM Maturity Model, and connect findings to broader scholarly and industry literature. The central question is: “What are the primary barriers encountered by Startup X in improving the maturity of risk management strategies?”

## **Findings**

### ***Barrier 1: Insufficient Training***

“I had one training session on risk management, but it wasn’t enough to apply it.” – Participant 2 (noted limited exposure to QRM and lack of practical follow-up).

Training emerged as the most consistent root barrier. Staff reported that QRM training was minimal, delayed, and lacked practical application. This lack of training explains why documentation was misunderstood, processes were inconsistently implemented, and cultural resistance persisted. In Waldron’s terms, this is Level 1–2, where training is ad hoc and reactive, blocking progression to Level 3, which requires structured, scenario-based learning.

### ***Barrier 2: Weak Governance and Leadership Commitment***

“We don’t really have a governance structure like the model outlines.” – Participant 3 (highlighted lack of formal structures and unclear accountability).

“Our director actually asks to see our risk logs. That’s new.” – Participant 1 (acknowledged some leadership attention, though only recently and inconsistently, which suggests high turnover rate).

Another root barrier is the absence of a formal QRM governance structure and inconsistent leadership commitment. Participants described governance as nonexistent, with risk responsibilities unclear and leadership involvement episodic. This barrier drives documentation gaps, weak process implementation, and resource neglect. In Waldron’s model, governance is essential for Level 3+ maturity, but Startup X remains stuck at Level 2.

***Barrier 3: Resource Constraints***

“We had to share one license between multiple people—it caused delays.” – Participant 2 (described specific IT/HR software tool limitations that slowed implementation).

Resource limitations—including insufficient staffing, lack of tool access, and IT bottlenecks—directly constrained QRM practice. This upstream barrier caused downstream effects such as weak process implementation (staff lacked time/tools to use risk registers) and contributed to cultural resistance (teams cut corners when under pressure). This barrier is typical of Level 2 maturity, where infrastructure is lacking to sustain consistent execution.

***Barrier 4: Cultural Resistance (Reinforcing Barrier)***

“Leadership says QRM is important, but we still cut corners to meet deadlines.” – Participant 3 (emphasized the tension between production pressures and QRM compliance).

Cultural resistance is both a barrier and a consequence of training and governance gaps. Without sufficient training or leadership modeling, QRM is perceived as bureaucratic rather than value-adding. This mindset perpetuates a reactive culture, anchoring Startup X in Level 2

maturity. Overcoming cultural resistance is necessary to move toward Level 4, where risk culture is proactive and embedded.

***Consequence: Documentation Gaps***

Fragmented and unclear SOPs are better understood as a symptom of weak governance and insufficient training. Without clear ownership and well-trained staff, SOPs become inconsistent and unreliable. According to interview participants, SOPs lacked defined escalation pathways and often existed in multiple, conflicting formats. This reflects Level 2 maturity, where processes are present but inconsistent, leaving staff without confidence in their use. Without closing this gap, achieving higher maturity levels that demand structured governance is impossible. Additionally, it is important to understand that the barrier is not the documentation itself, but rather the governance and training frameworks that should support it.

***Consequence: Patient Safety Risks***

Similarly, patient safety risks are consequences of barriers in training, governance, and culture. Inconsistent risk review was not the root problem but the result of staff being undertrained, processes poorly enforced, and leadership being inconsistent. Patient safety outcomes are compromised when barriers upstream remain unaddressed. Participants admitted that an inconsistent risk review placed product batches at risk. At Waldron's Level 1–2, patient safety is reactive and vulnerable to gaps in practice. Therefore, Startup X has demonstrated that it cannot safeguard patient outcomes or progress toward Level 4–5, where safety is systematically integrated.

**Table 4: Strategic Barrier Map - Waldron’s Model**

<b>Barrier</b>	<b>Waldron Level Indicator</b>	<b>Impact on Maturity</b>	<b>Outcome</b>
Insufficient Training (Root)	Level 1–2	Blocks skill development	Staff unable to apply QRM, SOP confusion, Documentation gaps, Patient Safety Risks
Weak Governance & Leadership (Root)	Level 2	No accountability, episodic support	Documentation gaps, Poor implementation, Patient Safety Risks
Resource Constraints (Root)	Level 2	Infrastructure lacking	Staff delays, risk registers unused
Cultural Resistance (Reinforcing)	Level 2	Reactive mindset persists	Cutting corners, compliance focus, Patient Safety Risks

**Evaluation of the Outcomes**

The project aimed to assess the maturity of Quality Risk Management (QRM) practices at Startup X using Waldron’s (2017) QRM Maturity Model. The goal was to determine the organization’s current stage of QRM maturity, identify specific barriers, and offer actionable recommendations to improve governance, training, and patient safety.

*Comparison of Planned vs. Actual Achievements*

The goal was to perform a diagnostic assessment of Startup X’s QRM maturity and establish a foundation for recommendations to improve practice. This was achieved: the results clearly placed Startup X at the emerging/early-developing stages (Levels 1–2), with evidence of immature documentation, inconsistent use of QRM tools, weak governance due to leadership turnover, and limited resources. Although the long-term goal of increasing maturity was outside the project's scope, the study successfully provided a validated assessment and a detailed roadmap for growth, aligning outcomes with the original objectives.

### *Impact, Benefits, and Changes*

The outcomes have immediate value for Startup X and potentially broader influence for early-stage CDMOs. At the organizational level, the results provided management with clarity on systemic weaknesses—transforming vague frustrations into concrete, actionable priorities such as establishing governance charters, embedding patient-safety considerations in risk registers, and instituting training programs. For individuals, the recommendations highlight how staff competence and safety culture can be strengthened through scenario-based training and non-punitive reporting systems. At the industry level, the work underscores common startup CDMO risks and positions Startup X to become more competitive by aligning with client expectations for advanced QRM practices. At a societal level, the ultimate benefit is enhanced patient safety, as stronger QRM systems reduce the likelihood of errors reaching the clinical environment.

### *Short, Intermediate, and Long-Term Outcomes*

- **Short-term outcomes** include the establishment of formal governance (QRM Charter, named risk owners, monthly reviews) and initiation of staff training. These actions provide immediate structure and visibility.
- **Intermediate outcomes** involve staff training programs, embedding QRM tools into workflows, cultural shifts through leadership walkrounds and safety campaigns, and consistent use of CAPA and risk registers. These will strengthen organizational competence and accountability.
- **Long-term outcomes** envision Startup X transitioning to higher levels of QRM maturity (Levels 3–4), characterized by sustainable governance, continuous

improvement cycles, and a proactive safety culture. This trajectory not only supports regulatory compliance but also advances strategic resilience and patient protection.

Overall, the project accomplished its intended diagnostic purpose and paved the way for Startup X to improve its QRM maturity. Its results offer both immediate benefits for the organization and long-term potential for industry and patient impact.

### **Connection to the Pharmaceutical market**

The observed challenges are **characteristic of early-stage CDMOs** facing commercial and time pressures:

- Documentation instability
- Minimal QRM emphasis in training
- Leadership inconsistency

These issues reflect broader industry findings about immature CDMOs struggling with governance clarity, cross-functional risk communication, and routine risk tool usage.

Additionally, the findings directly confirm the problem statement, with Waldron's model validating Startup X's early maturity stage, and market connection indicating these are common startup CDMO weaknesses that, if addressed, can boost maturity and competitiveness. Therefore, the analysis supports a practical action plan: aligning Startup X's QRM practices with recognized best practices and continuous improvement cycles (e.g., Plan–Do–Check–Act, standardized audits, cross-functional governance).

## **Action Plan**

Based on the project findings, the following action plan outlines the steps required to move Startup X from emergent practices toward defined and managed levels of QRM maturity. It addresses the variance between actual maturity and desired outcomes, and incorporates goals, objectives, responsibilities, resources, measurements, and timelines.

### ***Goals and Objectives***

The overarching goal is to transition Startup X from emergent/early-developing (Levels 1–2) to defined maturity (Level 3). Specific objectives include:

- Establishing formal and sustainable governance via a QRM charter and committee.
- Embedding QRM tools into daily workflows, ensuring risk registers are active and auditable.
- Developing staff competence through tiered training curricula and scenario-based exercises.
- Making patient-safety impact assessments explicit in all risk registers by integrating patient safety into decision-making.

### ***Responsibilities and Resources***

- **Executives** will approve the governance charter and allocate resources.
- **QA Director** will chair the governance committee and oversee training programs.

- **QRM Coordinator** will maintain risk registers, dashboards and coordinate audits.
- **Cross-functional teams** will monitor risks, review CAPAs, and ensure process adherence.

Resources include budget allocations for training, full licensing for QMS software tools, IT support agreements, and designated QRM staff capacity.

### **Measurements and Metrics**

Progress will be tracked using key performance indicators (KPIs):

- Percentage of SOPs with assigned owners and timely review.
- Risk register utilization rate.
- Percentage of CAPAs closed within deadlines.
- Staff training on QRM Competency completion and demonstration rates.
- Safety climate survey scores.

### **Communication of Findings**

Project findings will be communicated to internal stakeholders through governance meeting minutes, executive leadership briefings, and staff workshops. Externally, Startup X will report QRM maturity progress during client audits and regulatory inspections, reinforcing credibility, transparency, and competitive advantage.

### **Gantt Chart**

A Gantt chart will be developed (sample can be found in the Appendix) to map action steps across immediate (0–3 months), short (3–6 months), medium (6–12 months), and long-term

(>12 months) milestones across governance, training, process implementation, culture, and continuous improvement

### **Implications and Recommendations for Practice**

The findings have implications beyond Startup X. For hospitals and pharmaceutical consumers, supplier immaturity in QRM presents risks to product safety and patient outcomes.

Two key practice recommendations emerge:

- ***Independent QRM maturity audits:*** Hospitals and clients should require CDMOs to undergo independent assessments before finalizing quality agreements. This provides external validation of governance and process maturity.
- ***Strengthened quality agreements:*** Contracts should require evidence of active risk registers, standing governance committees, and competency-based training programs before production begins.

These recommendations connect with applied theories linking safety culture in healthcare (Leape et al., 2009; Pronovost et al., 2006) to manufacturing safety outcomes. However, their relevance should not be overstated—they are most applicable for early-stage CDMOs experiencing rapid growth. Furthermore, it is imperative to note that Startup X's barriers are rooted in insufficient training, weak governance, leadership inconsistency, and limited resources. These deficiencies are reinforced by a culture that undervalues proactive risk management. Addressing these barriers requires interventions at both the structural and cultural level. Focusing only on downstream symptoms—such as documentation gaps or audit irregularities—will not achieve sustainable progress. Instead, Startup X must invest in upstream solutions: formalizing

governance, building organizational competence, ensuring stable leadership commitment, and allocating resources for QRM infrastructure.

As such, the next steps for Startup X extend beyond correcting tactical deficiencies. They involve embedding QRM into the organizational identity, much like patient safety has been institutionalized in healthcare systems. By combining structured governance, competency-based training, explicit patient-safety focus, and cultural reinforcement, Startup X can move from a reactive posture toward a proactive, patient-centered model of QRM maturity. This not only addresses regulatory and client demands but also builds long-term strategic resilience in the competitive CDMO market. Therefore, it is imperative to consider the following:

#### ***Broader Implications – Learning from Hospitals and Healthcare Systems***

Hospitals and healthcare systems provide a useful benchmark for how QRM principles can translate into patient safety outcomes. In healthcare, patient safety movements have emphasized leadership visibility, non-punitive reporting cultures, structured incident analysis, and systematic training (Leape et al., 2009; Pronovost et al., 2006). These practices mirror the needs identified at Startup X.

***Leadership Walkrounds:*** In hospitals, senior leaders routinely visit units to discuss safety risks with staff (Frankel et al., 2003). Startup X can adapt this by having executives attend manufacturing floor meetings to reinforce QRM priorities.

***Safety Climate Surveys:*** Healthcare systems assess cultural readiness through validated staff surveys. Startup X could implement periodic QRM climate surveys to monitor progress.

***Incident Learning Systems:*** Hospitals use root cause analysis and morbidity/mortality reviews. At Startup X, a parallel approach would be structured RCA workshops after deviations, feeding into CAPA cycles.

***Standardization and Checklists:*** The WHO surgical safety checklist (Haynes et al., 2009) transformed surgical risk management. For startups, pre-mortem checklists before product release can serve a similar role, embedding patient safety in daily operations.

### **Recommendations for Future Research Projects and Startups**

Future research should expand upon the strengths and limitations of this project, particularly in relation to how hospitals and healthcare systems manage patient safety and the ways in which startups can adopt these practices. These directions address both observed barriers and broader structural challenges faced by CDMOs:

- **Embed Patient Safety as a Core Value:** Position patient safety alongside compliance and cost in strategic objectives. This aligns CDMO operations with client and regulatory expectations.
- **Adopt Continuous Learning Cycles:** Use the Plan-Do-Check-Act model to create learning loops from deviations, audits, and pre-mortems.
- **Leverage External Benchmarks:** Benchmark QRM maturity against both pharmaceutical peers and healthcare safety models to track improvement.
- **Build Resilience through Redundancy:** Just as hospitals design for fail-safe systems, startups should plan for leadership churn and resource shortages by institutionalizing governance roles and training pipelines.

Suggested directions include:

- **Comparative studies** examining QRM maturity across multiple startup CDMOs to identify common barriers and best practices.
- **Longitudinal research** tracking Startup X's improvement after implementing the action plan, providing evidence of sustainability.
- **Resilience strategies.** Given leadership turnover and resource shortages, studies should explore scalable governance structures and digital QMS tools for startups.
- **Policy studies.** Research into standardizing QRM maturity assessments as part of supplier qualification processes could strengthen industry-wide safety.

## Conclusions

The findings of this study directly support the central issue of limited QRM maturity among startup CDMOs. At Startup X, participants consistently described immature processes and documentation, inconsistent use of QRM tools such as risk registers and escalation pathways, governance disruptions caused by leadership turnover, and resource shortages that limited corrective actions. These themes confirm the problem statement: early-stage CDMOs struggle to establish reliable and sustainable QRM systems, exposing both compliance vulnerabilities and patient safety risks.

Mapped against Waldron's (2017) QRM Maturity Model, the evidence positions Startup X between Levels 1 and 2, reflecting an emergent to early-developing stage. Interview data revealed unclear escalation roles, inactive risk registers, irregular audits, and fragile governance structures. Such gaps indicate a reactive rather than proactive culture of risk management, underscoring that Startup X has not yet achieved the structured governance, training, and learning cycles associated with higher maturity levels (Levels 3–5). While there are signs of

leadership engagement and rising awareness, these are undermined by systemic weaknesses, leaving QRM practices fragile, inconsistent, and largely compliance-driven.

These findings also mirror patterns documented in the broader CDMO literature, where fragmented governance, reactive approaches, and underinvestment in training and infrastructure hinder QRM maturity (ICH Q9, 2005; ISPE, 2015; Waldron, 2017). Regulatory and scholarly perspectives further emphasize that sustainable maturity requires more than documents—it depends on leadership continuity, governance stability, and cultural integration (FDA, 2021; EMA, 2019; Reason, 2000; Leape et al., 2009). Startup X’s challenges therefore represent both internal weaknesses and strategic risks in a market where clients increasingly demand QRM excellence.

The recommendations developed in this study directly address these gaps, offering a roadmap to strengthen governance, embed training, reinforce implementation, and integrate patient safety. If implemented, these steps can help Startup X progress from its current reactive, fragile practices (Levels 1–2) toward more structured, managed maturity (Levels 3–4). The barriers identified—weak governance, limited resources, insufficient training, and cultural resistance—are both root causes of immaturity at Startup X and common challenges across the CDMO sector. Addressing these at their source is essential for sustainable improvement.

Overall, the study confirms alignment between the problem, purpose, and need of this dissertation. By situating Startup X within Waldron’s framework and linking the findings to industry-wide trends, the analysis provides diagnostic clarity and a foundation for actionable recommendations. Startup X’s current maturity gaps are not mere inefficiencies but significant compliance, safety, and strategic risks. The proposed action plan is therefore critical to advancing

the organization from reactive practices toward structured governance, cross-functional learning, and a patient-centered QRM maturity framework.

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## **Appendices**

Appendix A: Interview Protocol

Appendix B: QRM Documentation Assessment

Appendix C: Detailed Startup X Action Plan defined with Metrics, Sample Template and Training curriculum

Appendix D: Hospital Patient Safety Practices and Recommendations for Startup Implementations

Appendix E: Gantt Chart of Startup X Action plan

## **Appendix A: Interview Protocol**

*The QMM interview protocol should offer a structured, objective approach to evaluate Startup*

*X's level of maturity in the five practice areas below:*

1. *Management Commitment to Quality*
2. *Business Continuity*
3. *Advanced Pharmaceutical Quality System (PQS)*
4. *Technical Excellence*
5. *Employee Engagement and Empowerment*

***Responses to the interview questions should aim to give the researcher an insight into the following:***

- *Management's commitment to quality sets the tone for the entire organization, ensuring that quality is prioritized, aligned with business objectives, and resourced appropriately.*
- *Business continuity ensures operational resiliency, safeguarding against disruptions and minimizing risks to the supply chain.*
- *An advanced PQS takes advantage of learnings gained across products and from all stages of the product lifecycle to optimize process performance and product quality.*
- *Technical excellence promotes the acquisition of new skills and the implementation of advanced manufacturing and analytical methods that are fit for purpose, driving operational excellence.*
- *Finally, employee engagement fosters a culture of quality throughout the organization, empowering employees to actively contribute to continual improvement and patient safety.*

*Format:*

*Thank you for agreeing to talk about your experiences working with the Quality Risk Management (QRM) strategies and procedures in your organization.*

*First, just a little background...*

[Do Not Read] Section 1: Background Information

1. **Can you describe your role and responsibilities in your current/past position as it relates to the Quality Control testing of Drug Substances and Drug Products at Startup X?**

Follow-up: What specific tasks do you perform related to quality risk management (QRM) at any point in the Drug Manufacturing Process?

2. **Have you received any formal training on QRM procedures?**

Follow-up: 3[IF YES] how would you describe that training? Was it sufficient to understand and apply QRM principles in your daily work?

*Thank you for providing that background.*

3. **Do standardized procedures exist for drug product transfers between different Startup X sites and clinics, or hospitals, to ensure a fast, stable, and compliant knowledge transfer?**

Follow up: How long have you been involved in said procedures and overall QRM-related activities?

4. **Does Startup X regularly survey and implement stakeholder recommendations?**

Follow up: How are you involved in such activities?

- 5. Is/Was your department closely linked to and consistent with the overall company corporate objectives of Start Up X to meet shareholders' standards, with a clear focus on patient safety?**

Follow up: What are the ultimate goals and objectives of the Quality unit that you work/worked in?

[Do Not Read] Section 2: Perceptions of Documented QRM Procedures

*Regarding the documented QRM procedures here at your organization.....*

- 6. Can you briefly describe the key QRM procedures that are documented in your organization?**

Follow-up: How do you access these procedures (e.g., manuals, online portals, SOPs)?

- 7. Do you feel that the QRM strategies documented are aligned with the organization's overall goals for patient safety and product quality?**

**In your view, how effective are the QRM strategies that have been documented?**

Follow-up: Why do you think they are effective (or ineffective)?

- 8. From your perspective and experience, how clear are the instructions or guidelines provided in the QRM documentation?**

Follow-up: Can you think of a specific example where the instructions are/were unclear or difficult to follow?

[Do Not Read] Section 3: Actual Implementation of QRM Strategies

*I realize in your work that documented QRM procedures may not always be implemented as planned.....*

**9. How do the current Risk Assessment strategies that you employ affect the potency of the drug product (i.e., the ability of the product to yield a given result for stakeholders)?**

Follow-up: Are these procedures outlined in your QRM strategy integrated into your regular tasks, or are they seen as separate or additional?

**10. Can the current Risk Assessment strategies potentially impact the sterility or stability of the drug product?**

Follow-up: How do the current Risk Assessment strategies impact the general performance of your analytical methods? Can you think of any situations where it would be challenging to follow the documented procedures to achieve optimal results?

**11. In your experience, to what extent are the QRM procedures followed as they are documented?**

Follow-up: If there are any deviations, what are the reasons for not following the prescribed procedures?

*Thank you for sharing your experience and insight.*

[Do Not Read] Section 4: Support and Resources for QRM Implementation

*I have a few questions regarding the resources available to technicians for implementing QRM strategies effectively.*

**12. Do you feel that you have the necessary resources and tools to implement the QRM procedures effectively?**

Follow-up: What specific resources (e.g., equipment, training, time) would help you implement QRM more effectively?

**13. Are there regular checks or audits to ensure that QRM procedures are being followed?**

Follow-up: How do these audits or checks impact your work? Are they helpful in ensuring compliance?

**14. What method of root cause analysis is employed at Start-up X?**

Follow up: Are there standardized tools to get a deeper understanding of the influencing factors for any manufacturing or quality problems that may arise with the Drug Product/Drug Substance?

**15. Are all potential bottlenecks generally pre-identified before the drug manufacturing process begins at the CDMO?**

Follow up: How does that impact the Quality Control Department that you work/worked in? What data exists that supports the current performance status, as it relates to QRM maturity progression at Startup X?

*Thank you this feedback.*

[Do Not Read] Section 5: Overall Evaluation and Recommendations

*Just a few more questions and a opportunity for you to help improve the process.*

**16. From your perspective, how well does the current QRM system protect the patient and improve the quality of medicinal products?**

Follow-up: Do stakeholders, in collaboration with Startup X have joint improvement programs to increase performance and quality procedures? What are the specific areas involved?

**17. If you were to suggest one key improvement to the QRM strategy or its implementation, what would it be?**

Follow-up: How would this change improve the process or its outcomes?

**18. Do you think that the QRM procedures as documented are continually improving?**

Follow-up: How can the organization ensure that the QRM processes evolve and adapt to new challenges?

*I want to thank you for your time and for your thoughtful responses. The perspectives you have shared have been very insightful and helpful. In closing,*

[Do not Read] Closing Remarks

**19. Is there anything else you would like to share regarding your experience with QRM implementation in your role?**

**20. Do you have any questions?**

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**Appendix B: QRM Documentation Assessment of Startup X SOPs and Related  
Documentation**

***Category 1. Documentation Clarity***

<b>Sub-dimension</b>	<b>Assessment Level (1–4)</b>	<b>Justification</b>
Clarity of Purpose	2	The SOPs reference patient safety and quality but fail to articulate how QRM contributes to Startup X’s strategic or regulatory objectives. Alignment with organizational goals is weak.
Procedure Description	2–3	Risk assessment and escalation procedures are outlined but lack comprehensive step-by-step guidance. Tools and templates are missing, leading to inconsistent application.

***Category 2. Completeness of Documentation***

<b>Sub-dimension</b>	<b>Assessment Level (1–4)</b>	<b>Justification</b>
Scope of Procedures	2	SOPs cover risk identification and assessment but provide little guidance on mitigation, communication, or ongoing review. Near-miss reporting and continuous monitoring are absent.
Regulatory Alignment	2	Documentation makes limited reference to ICH Q9 and FDA standards but does not explicitly embed these requirements within procedures. Regulatory integration is incomplete.

***Category 3. Effectiveness of QRM Strategy***

<b>Sub-dimension</b>	<b>Assessment Level (1–4)</b>	<b>Justification</b>
Risk Identification & Assessment	2–3	Tools such as risk registers exist, but they are dormant or inconsistently applied. There is no standardized scoring methodology across functions.
Risk Control & Mitigation	2	Corrective actions are occasionally documented, but preventive actions and structured mitigation frameworks are absent. CAPA closure is inconsistent and delayed.

**Category 4. Accessibility and Usability**

Sub-dimension	Assessment Level (1–4)	Justification
Document Accessibility	2–3	Documentation is stored digitally but suffers from inconsistent version control and incomplete licensing for QMS tools. Accessing the most recent SOPs is difficult for some staff.
Document Usability	2	SOPs are often lengthy, inconsistently formatted, and lack practical examples. Usability for frontline staff is low, particularly for complex risk management tasks.

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**Overall QRM Documentation Assessment**

Category	Assessment Level	Narrative Summary
1. Documentation Clarity	2	Intent is evident but articulation of purpose is vague, and procedures lack sufficient detail.
2. Completeness of Documentation	2	Core elements of QRM are missing or underdeveloped; regulatory alignment is weak.
3. Effectiveness of QRM Strategy	2–3	Tools exist but are inconsistently applied; strategy remains reactive and fragmented.
4. Accessibility and Usability	2–3	Access is technically possible, but usability and version control issues undermine effectiveness.

**Overall Assessment:** Startup X’s SOPs and documentation reflect *novice-level maturity (Level 2)* with some elements approaching *intermediate maturity (Level 3)*. The documentation demonstrates intent but lacks clarity, completeness, and usability, reinforcing Startup X’s overall positioning at the early-developing stage of QRM maturity.

## Appendix C: Startup X Action Plan

### ***Startup X Action Plan defined:***

**A. Establish Formal Governance** (Priority: Immediate → Short. Please note that “Immediate” = high-priority initiation actions; “Short/Medium/Long” describe sequencing, not hard time estimates)

Weak governance is the primary structural blocker. Without clear ownership and escalation channels, SOP fixes and training will not be sustained.

#### **1. Establish a QRM Governance Charter (Immediate)**

- What: formal charter defining purpose, membership (QA, QC, Ops, MS&T, Clinical/Regulatory liaison), roles (risk owner, incident reviewer), meeting cadence, decision authority, and reporting lines to executive leadership/board.
- Who: Interim QRM Sponsor (senior leader) + QA Director to draft; CEO/COO to approve.
- Metrics: charter approved; committee roster published; first meeting minutes recorded.

#### **2. Designate Named Risk Owners & RACI for critical processes (Immediate)**

- What: assign owners for SOPs, risk registers, tech transfer, calibration, deviations. Create simple RACI matrix (Responsible/Accountable/Consulted/Informed).
- Metrics: every critical SOP has an owner; owners listed in the governance charter.

#### **3. Mandate Monthly Risk Review (Immediate → Short)**

- What: standing agenda item in governance meetings: open risks, CAPA status, high-priority escalations with owners and due dates in the risk register.
- Metrics: % of open risks with owner & next action; overdue risk %.

**Implication:** Formal governance turns episodic leadership interest into sustained accountability — a necessary move to Waldron Level 3 (Defined).

***B. Training & Competence (Priority: Immediate → Short → Medium)***

Training deficits explain many downstream failures (incorrect SOP use, ignored risk tools). Competence underpins culture change.

*Actions*

**1. Create a Tiered QRM Curriculum (Immediate)**

- Modules:
  - *Intro to QRM & ICH Q9 basics* (all staff)
  - *Operational QRM* (QC/OPS — applying risk registers, triggers)
  - *Leadership QRM Bootcamp* (executives — decision-making & sponsorship)
  - *Investigation & RCA* (QA/QC — root-cause analysis, human factors)
- Method: blended learning (scenario-based workshops + job aids).

Include short tests and practical assessments.

**2. Scenario-Based Practical Labs (Short)**

- Use real deviations and mock audits as training scenarios (e.g., simulated batch deviation, chain-of-custody lapse). Require a documented risk assessment and CAPA plan during the lab.

3. **Training Transfer Measures (Short → Medium)**

- Tie training to demonstration of competence: supervisors sign off on the on-the-job application (evidence: completed risk register; correct use of change control).
- KPIs: % staff certified; % competency demonstrations passed.

**Implication:** Structured training converts awareness into competence, moving the culture from reactive to preventive, a critical step toward Waldron Level 3–4.

***C. Process Implementation & Tools (Priority: Immediate → Short → Medium)***

Existing risk tools are present but unused. Embedding them in workflow makes QRM operational rather than theoretical.

*Actions*

1. **Re-launch a Simplified Risk Register (Immediate)**

- Minimal required fields: risk ID, description, source, likelihood x impact scoring, owner, mitigation, trigger(s), residual risk, due date, status.
- Make it visible to governance committee and included in monthly dashboards.

2. **Embed Risk Review in Core Workflows (Immediate → Short)**

- Batch kickoff checklist must include a risk review sign-off. Tech-transfer, change control, and CAPA processes require explicit risk register entries.

- Use a one-page template attached to each batch record.
3. **Adopt/Upgrade QMS Tools (Short → Medium)**
- Ensure reliable document control (MasterControl or equivalent), electronic deviations/CAPA, and a shared risk register. Prioritize covering necessary licenses and access controls.
  - Quick wins: enforce check-in/check-out controls on SOPs to avoid offline copies.
4. **Standardize RCA (Root Cause Analysis) & CAPA Workflows (Short)**
- Standard RCA templates, causal mapping (5-why or fault-tree), and CAPA tracking with evidence attachments. Require governance review before closure.

### **Metrics**

- Risk register utilization rate (% of active projects with risk register entries).
- % Deviations with RCA documented and CAPA tracked.
- Time-to-CAPA-closure (median) and % overdue.

**Implication:** Embedding tools into workflows makes QRM visible and auditable — crucial for moving from Level 2 → Level 3.

### ***D. Culture Change & Human Factors (Priority: Short → Medium → Long)***

Cultural resistance persists because staff see QRM as extra work without clear benefit. Culture change must be driven by leadership and reinforced through policies and incentives.

### **Actions**

1. **“Prevent Before Produce” Campaign (Short)**
  - Messaging: leadership front-line visits, celebrates examples where early risk identification prevented escalation.
  - Rewards: small recognition for staff who identify preventive actions.
2. **Psychological Safety & Speak-Up Channels (Short)**
  - Anonymous and named channels for raising risks; guarantee non-retaliation; publish outcomes of raised concerns to demonstrate closure.
3. **Human Factors Integration (Medium)**
  - Use basic human factors checks: procedure readability, ergonomics of data entry, workload assessments. Integrate human factor review into SOP approvals.
4. **Leadership Walkrounds & Safety Rounds (Short → Medium)**
  - Leaders perform regular rounds focusing on risk conversations; report learnings back to the governance committee.

### **Metrics**

- Staff survey: percentage who agree “I can raise safety concerns without retaliation.”
- % of preventive actions recorded vs corrective actions.

**Implication:** Culture initiatives increase reporting and prevention, key features of Waldron Levels 4–5.

### ***E. Resourcing & Infrastructure (Priority: Immediate → Short → Medium)***

Tooling and staffing constraints repeatedly blocked practice.

### **Actions**

1. **Immediate Audit of Tools & Licenses (Immediate)**
  - Inventory licenses, access issues, and critical missing tools; prioritize purchasing critical items (document control, electronic deviations).
2. **Designate QRM FTEs / Shared Functional Leads (Short)**
  - At least one QRM coordinator (shared across projects) to maintain registers, coordinate audits, and support training.
3. **IT & Access SLA (Short)**
  - Enforce rapid IT support for access and password-reset SLAs tied to production-critical roles.

### **Metrics**

- % of critical tools with full license coverage.
- QRM coordinator onboarded (Yes/No).
- SLA compliance (%).

**Implication:** Resource fixes remove operational delays and enable stable practice — precondition for sustained maturity.

### ***F. Performance Measurement & Continuous Improvement (Priority: Short → Medium → Long)***

Without measurement, improvement cannot be proven or guided.

### **Actions**

1. **Define QRM KPIs & Dashboard (Short)**
  - Example KPIs: Risk register utilization; % risks with owner & due date; % CAPAs closed on time; # preventive actions; staff QRM competence %.
2. **Annual Maturity Self-Assessment (Short → Medium)**
  - Use Waldron-aligned scoring to track progress across dimensions.
3. **PDCA Cycles (Medium)**
  - For each major process (SOP control, deviation handling, tech transfer), run small PDCA experiments and scale successful practices.

**Implication:** Measurement creates accountability and informs evidence-based scaling toward higher maturity.

***G. Patient Safety Integration (Priority: Immediate → Short)***

Patient safety is the ultimate outcome; integrate it explicitly in QRM.

**Actions**

1. **Patient-Safety Impact Field in Risk Register (Immediate)**
  - Every risk entry must include a “Patient Safety Impact” rating and mitigation tied to patient harm scenario.
2. **Clinical SME Involvement (Short)**
  - Where possible, involve a clinical subject-matter expert or pharmacist to validate safety-critical decisions (even via part-time advisory role).
3. **Pre-mortems for Critical Transfers (Short)**

- Before tech transfer or first batch release, hold a pre-mortem to anticipate potential failure modes and required actions.

## Metrics

- % risks with patient-safety impact assessed.
- Pre-mortems completed for first-time transfers.

**Implication:** Embedding patient-safety thinking aligns QRM decisions to patient outcomes and regulatory expectations.

## Sample Templates

A set of practical tools that support the *Executive Implementation Plan* above, as referenced within the text of the paper. Each subsection (A, B, C, etc.) is a different template that Startup X (or any CDMO) can use to operationalize QRM maturity.

- A. Minimal Risk Register → A template for the *core QRM tool* where risks are logged, assessed, and tracked.
- B. QRM Governance Charter → An outline for a *formal governance framework*, defining who owns QRM responsibilities and how decisions are made.
- C. Training Curriculum → A structured *staff training plan*, broken into tiers with objectives and assessments.
- D. Pre-mortem Checklist → A *checklist for proactive risk identification* before major events (e.g., tech transfer, first batch release).

### A. Minimal Risk Register (fields)

- Risk ID
- Risk Description
- Source/Trigger (Deviation, Change Control, Audit, Pre-mortem, etc.)
- Likelihood (Low/Med/High)
- Impact (Low/Med/High)
- Overall Score (L×I)
- Patient Safety Impact (Yes/No; Critical/Non-critical)
- Risk Owner (Name/Role)
- Mitigation Plan
- Residual Risk Score
- Status (Open/In Progress/Closed)

- Due Date / Closure Date

**B. QRM Governance Charter (outline)**

**Purpose:** Provide a framework for QRM oversight and decision-making.

**Scope:** Applies to all quality-affecting activities at Startup X.

**Committee Membership:** QA Director (Chair), QC Lead, Ops Lead, MS&T, Regulatory/Clinical Advisor, IT/Infrastructure.

**Roles & Responsibilities:**

- Approve risk methodology and tools
- Review open risks and CAPAs monthly
- Assign accountability for SOP ownership and risk register maintenance
- Report quarterly to Executive Leadership

*Meeting Cadence: Monthly formal meeting; ad hoc for escalations.*

*Decision Rights: Committee votes majority; Chair escalates to COO/CEO if unresolved.*

**C. Training Curriculum (tiers + objectives + assessments)**

Tier	Audience	Content	Objectives	Assessment
<b>Intro to QRM (All Staff)</b>	All employees	QRM principles, ICH Q9 basics, Startup X SOPs	Define QRM; recognize risk triggers	10-question quiz
<b>Operational QRM (QC/OPS)</b>	QC/Operations staff	Using risk registers, deviation handling, change control	Apply risk assessment to tasks	Risk register entry demo
<b>Leadership Bootcamp</b>	Executives & managers	Governance, decision-making, resource sponsorship	Lead governance meetings; resource planning	Mock governance scenario
<b>RCA &amp; CAPA Mastery</b>	QA/QC staff	Root cause analysis tools, CAPA lifecycle	Conduct RCA & draft CAPA	RCA case study

***D. Pre-mortem Checklist (for tech transfer / first batch)***

- Have potential failure modes been brainstormed (equipment, SOPs, training, labeling, supplier quality)?
- Were risks logged in the risk register with owner and mitigation?
- Has patient safety impact been explicitly rated?
- Are escalation pathways clear and documented?
- Have training records been reviewed and competency confirmed?
- Has QA approved documentation readiness (no gaps)?
- Was a cross-functional dry run conducted (simulation or tabletop)?
- Final sign-off by Governance Committee before release.

## **Appendix D: Hospital Patient Safety Practices and Recommendations for Startup Implementations**

### **Hospital patient-safety practices**

1. **Safety Culture Assessments (e.g., HSOPS)**
  - Regular staff surveys measuring safety climate, reporting culture, leadership support.
2. **Structured Incident Reporting & Learning Systems**
  - Near-miss and adverse event reporting systems with non-punitive policies and structured analysis (RCA).
3. **Multidisciplinary Safety Committees**
  - Hospital-wide committees that include clinical, nursing, pharmacy, and quality to review events and set priorities.
4. **Standardized Checklists & Protocols**
  - E.g., WHO surgical safety checklist; medication reconciliation.
5. **Simulation & Scenario Training**
  - Use of simulation for high-risk procedures and interprofessional drills.
6. **Human Factors & Ergonomics**
  - Use of HF design to reduce latent conditions that lead to errors.
7. **Executive Walkrounds & Visible Leadership**
  - Leaders regularly visit frontline settings to listen and act on safety concerns.

*A. An insight into How startups (CDMOs) can implement hospital-derived patient-safety practices*

### **1. Safety Culture Assessment → adopt a short “QRM Safety Climate” survey**

- Implement a brief quarterly survey adapted from HSOPS to measure: willingness to report, management support, and communication openness.
- Use results to prioritize culture interventions and measure improvement.

### **2. Structured Incident & Near-miss Reporting**

- Implement a low-barrier reporting tool (integrated into QMS or a simple form) that allows staff to report near-misses confidentially.
- Ensure follow-up (RCA, CAPA) and feedback loops — hospital practice shows that learning happens only if the reporter sees action.

### **3. Multidisciplinary QRM Committee (modeled on hospital safety committees)**

- Include QC, QA, manufacturing, regulatory, clinical pharmacist/advisor, and operations.
- Meet regularly to review incidents, safety metrics, and prioritize system changes.

### **4. Standardized Safety Checklists & SOP readbacks**

- Use checklists for high-risk transitions: tech transfer, first batch release, shipping to clinic.
- Require readbacks or oral confirmations for critical steps to reduce miscommunication.

### **5. Simulation & Scenario-based Drills**

- Run tabletop pre-mortems and small simulations of deviations (e.g., mislabeled vials, chain-of-custody breaches) to train staff and test processes before events occur.

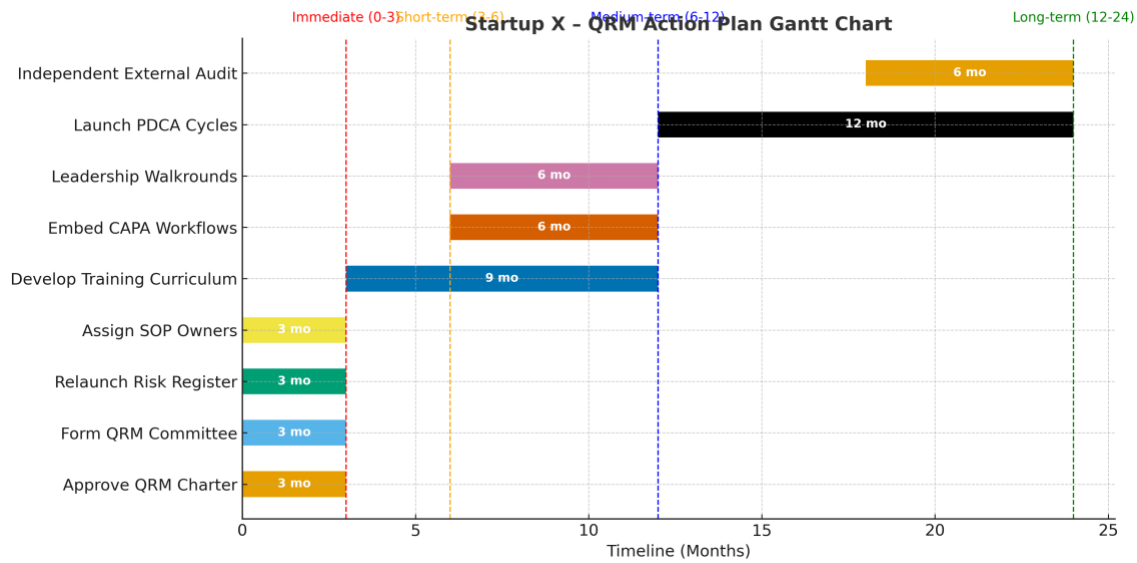
## **6. Human Factors Review in SOP design**

- Apply simple HF checks: readability, font size, step clarity, cognitive load.
- Include HF review as an approval gate for SOPs and new equipment.

## **7. Executive Walkrounds & Visible Leadership**

- Leaders schedule regular walkrounds, ask structured questions about risk, and report back actions taken. This is high-impact for culture change.

## Appendix E: Gantt Chart of Startup X Action Plan



Startup X QRM Action Plan Gantt Chart

### Timeline

- **Immediate (0–3 months):** Charter approval, committee creation, relaunch of risk register, assign SOP owners.
- **Short-term (3–6 months):** Training curriculum design begins.
- **Medium-term (6–12 months):** CAPA workflow embedding, training rollout, leadership walkrounds.
- **Long-term (12–24 months):** PDCA cycles, external audits.

### Gant Chart Data

Category	Action Item	Start (Month)	End (Month)	Duration
<b>Governance</b>	Approve QRM Charter	0	3	3 mo
	Form QRM Committee	0	3	3 mo
<b>Process Implementation</b>	Relaunch Risk Register	0	3	3 mo
	Assign SOP Owners	0	3	3 mo
<b>Culture &amp; Training</b>	Embed CAPA Workflows	6	12	6 mo
	Develop Training Curriculum	3	12	9 mo
	Leadership Walkrounds	6	12	6 mo
<b>Continuous Improvement</b>	Launch PDCA Cycles	12	24	12 mo
	Independent External Audit	18	24	6 mo

***Interpretation:***

The Gantt chart illustrates Startup X's phased QRM action plan across immediate, short-term, medium-term, and long-term horizons. In the immediate stage (0–3 months), Startup X is tasked with foundational governance actions, including the approval of the QRM Charter, formation of a QRM Committee, relaunch of the risk register, and assignment of SOP owners. Short-term actions (3–6 months) initiate the development of a training curriculum, laying the groundwork for culture and competence building. Medium-term activities (6–12 months) focus on embedding CAPA workflows into operations and conducting leadership walkrounds to strengthen safety culture. Finally, long-term actions (>12 months) include launching continuous PDCA cycles and commissioning an independent external audit to verify maturity progress. The sequencing demonstrates a logical progression from governance establishment to cultural integration and sustained improvement, aligning with Waldron's (2017) QRM Maturity Model trajectory.