M. Sc. Dissertation

Implementation of a Quality Risk Management Approach to Commissioning and Qualification in the Biopharmaceutical Industry

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This project is submitted in part fulfilment of the HETAC requirements for the award of Master of Science in Biopharmaceutical Science.

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ABSTRACT

Inefficient, traditional C&Q practices and a more recent regulatory focus on the application of risk assessment to pharmaceutical processes, assessing impact on product quality and the protection of the patient, have led to a new approach to C&Q. Commissioning and qualification is an integral part of the Process Validation Lifecycle and, if not executed efficiently, can contribute to increased costs and schedule delays in delivering facilities that are fit for their intended use.

The focus of this research is to map the current implementation of Quality Risk Management and risk-based C&Q, to assess the benefits of risk-based C&Q and to analyse the obstacles to its implementation in the biopharmaceuticals industry.

The research methods adopted in this dissertation consists of an extensive literature review, a comprehensive review of recent conference proceedings and a set of focused interviews with five biopharmaceutical industry Subject Matter Experts with a range of experience in C&Q in the biopharmaceuticals industry.

The findings from the research show that the implementation of risk-based C&Q is at an early stage in the industry, that up to now the industry has focused too firmly on risk assessment tools at the expense of Quality Management Systems and that the industry faces a challenge in implementing the requisite supporting practices and in making the organisational and operational changes necessary to successfully execute risk-based C&Q.

This dissertation recommends that senior management need to take greater ownership of the Quality Risk Management programme and run it as a site-wide programme. Organisations need to become more proficient at a wider range of risk assessment tools and practices and it also recommends that companies adopting a risk-based approach need to upgrade their programmes in the supporting practices of Good Engineering Practice, Design Review and Change Management.

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Declaration of Originality:

"I hereby declare that this project is entirely my own work and that it has not been submitted for any other academic award, or part thereof, at this or any other education establishment".

Signed Eamon O'Connor

Date 31 May 2012

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I would like to thank my wife, Olive for her endless patience. I would also like to thank my supervisor Karen Quigley for her help, encouragement and insightful feedback. I would finally like to thank my five interviewees for being so generous with their time and their expertise.

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1.0 INTRODUCTION AND RESEARCH METHODS

1.1 Background

Since the concept of process validation was first outlined by the FDA in 1987 (FDA, 1987), uncertainty over the requirements for regulatory compliance has led biopharmaceutical companies to adopt increasingly onerous commissioning and qualification (C&Q) practices, which has driven an increase in the cost of new facilities (ISPE, 2001).

Current commissioning and qualification practices are largely based on the ISPE Baseline Guide 5, which was issued in March 2001 (ISPE, 2001). This document was written against a backdrop of increasing costs and lead times for bringing new facilities online. Cost and schedule overruns were being driven by "inconsistent interpretations of regulatory requirements" (ISPE, 2001). The ISPE also anticipated that the guide would offer "consistent interpretation" of regulatory requirements and would "facilitate timely and cost effective commissioning and qualification" (ISPE, 2001).

Baseline Guide 5 (BG5) became the industry standard approach to C&Q and outlined the now familiar structure of sequential C&Q processes: Impact Assessment, Commissioning, Installation Qualification, Operational Qualification and Performance Qualification. The guide also described the two key supporting processes, Good Engineering Practices and Enhanced Design Review. Baseline Guide 5 introduced the first risk-based approach to C&Q by recommending the performance of Impact Assessments as a means of focusing effort on critical systems. Later guidance documents, however, have offered a very different and far more comprehensive vision of the type of risk management required in the biopharmaceuticals industry.

In 2004, the FDA issued a significant new document: "Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach" (FDA, 2004). In this document the FDA stated that it

had "identified a risk-based orientation as one of the driving principles of the cGMP initiative" (FDA, 2004).

This document signalled a major shift in direction for the industry regarding Quality Risk Management. The document stated that risk-based and science-based approaches to regulation of product quality were the guiding principles of the initiative. Quality Risk Management of pharmaceutical products had now moved to centre stage in the industry and was now recommended as a guiding principle in Current Good Manufacturing Practice.

Arising out of the FDA initiative, in 2005, the ICH issued "Quality Risk Management" (ICH Q9) which described a systematic approach to Quality Risk Management. This document is the basic industry guide to Quality Risk Management in the Biopharmaceuticals industry. It defined Quality Risk Management as "a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle" (ICH, 2005).

ICH Q9, in conjunction with ICH Q8 (Pharmaceutical Development) and ICH Q10 (Pharmaceutical Quality System), form the basis for the new science and risk-based approach to pharmaceutical development and manufacture. ICH Q9 defines the guiding principles of Quality Risk Management as:

- "The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient"
- "The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk"

(ICH, 2005).

ICH Q9 is a general document that can have many potential applications in the industry. This research will focus on Quality Risk Management for the commissioning and qualification of Facilities, Equipment and Utilities.

The vision of risk management presented in ISPE Baseline Guide 5 was very much focused on equipment in what is known as a "bottom-up approach" as described in the ISPE Good Practice Guide (2011), but ICH Q9 presented a vision of risk management which focused on scientific knowledge and the risk to the safety of the patient in what is known as a "top-down

approach". This fundamental paradigm shift for the industry forms the backdrop for this research.

In 2007, the ASTM E2500 guideline "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment" took these guiding principles and applied them to the specification, design and verification of manufacturing systems (ASTM, 2007). In this standard, C&Q has evolved into a new process called verification and the methodology of verification of suitability for intended use is significantly different.

More recently, in 2011, the ISPE has issued further guidance in the form of two draft documents: Baseline Guide 12; "Science and risk based-approach for the delivery of Facilities, Systems, and Equipment" (ISPE, 2011) and a Good Practice Guide; "Applied Risk Management for C&Q" (ISPE, 2011). A fundamental shift in thinking regarding C&Q practices has taken place in the last ten years in the biopharmaceuticals industry. The system-based C&Q approach of Baseline Guide 5 is being replaced by the science and risk-based approach defined by the FDA, ICH, ISPE and ASTM. The FDA Process Validation guideline, issued in 1987, was updated in 2011 and reflects the updated thinking regarding "the use of modern pharmaceutical development concepts, quality risk management and quality systems at all stages of the manufacturing process lifecycle" (FDA, 2011, p.1). The new thinking in the industry involves approaching a product from a holistic, lifecycle point of view and using the science and risk-based concepts throughout the entire lifecycle. The process validation guideline also serves to clearly explain where C&Q sits in the overall lifecycle.

But why should companies adopt a new approach? The ISPE suggest many advantages can be realised by the new approach. Fundamentally they suggest that patients can benefit "through a reduction of risk and an improvement in real-world quality" (ISPE, 2011, p.11). They suggest that manufacturing organisations can also benefit through "significantly reduced costs and time compared to traditional C&Q", "more consistent and reliable achievement of end-user requirements", "improved process knowledge as a basis for

subsequent operations" and "improved alignment with post-ICH Q9 regulatory expectations" (ISPE, 2011, p.11).

1.2 Research Focus

Implementation of Quality Risk Management is the basis for the new science and risk-based approach. Adopting the new science and risk-based approach will require changes from all of the C&Q stakeholders as the methodology is significantly different, the terminology is different and the organisational structures required to successfully execute the new approach are also different.

It has become clear from recent conference proceedings and journal articles that the biopharmaceutical industry has begun to adopt the science and risk-based approach in some engineering projects in the last two or three years. It is clear that there is a need to examine these initial attempts to determine their success or otherwise. By critically evaluating the reported results, conclusions can be drawn which may serve as valuable lessons for the entire industry as it adopts the new approach.

Commissioning and qualification of manufacturing equipment and facilities is a critical activity in the overall process validation lifecycle. C&Q represents a significant technical challenge to all biopharmaceutical companies and requires time and resources in order to execute. BG5 C&Q practices have become well established in the industry in the past decade and practically all biopharmaceutical companies have put structures in place which align with this guideline. Moving away from the Baseline Guide 5 C&Q approach thus presents a challenge to the biopharmaceuticals industry.

In particular the research will examine the impact that implementation of a risk-based approach had on C&Q practices. The research will evaluate the impact of the new approach on team structures, team member responsibilities, commissioning and qualification methodology and on supporting processes such as change control and good engineering practice.

1.3 Research Objectives and Methods

This dissertation will focus on the development of Quality Risk Management in C&Q practices in the biopharmaceutical industry since 2001 when BG5 was issued. Why should a company consider implementing Quality Risk Management based C&Q practices as defined in ICH Q9? How does a company go about doing this? What is the current status of Quality Risk Management and risk-based C&Q in the Biopharmaceuticals industry? What form has Quality Risk Management taken in its implementation? How well is the current implementation of QRM aligned with ICH Q9? Have any particular difficulties been encountered and have any benefits been realised in the resulting C&Q practices?

The overall aim of this research is to advance an understanding of the implementation of both Quality Risk Management and risk-based commissioning and qualification practices. The driver for the industry changes is new guidance issued by the FDA regarding the importance of a science and risk-based approach in ensuring product quality (FDA 2004, 2011).
The research will look firstly at the standard industry guidance documents that form the basis of the C&Q approaches of all biopharmaceutical companies. This research will examine this industry guidance and highlight the practical changes required of companies in order to comply.

Furthermore, a major focus of this research will be to study the reported cases of implementation of Quality Risk Management-based C&Q and to critically evaluate the reported results. A further research method will be employed involving focused interviews with Biopharmaceutical Industry C&Q Subject Matter Experts.
The objectives of this research are to:

1. Trace the development of both commissioning and qualification and risk management practices over the last 25 years.
2. Describe the Quality Risk Management process as it applies to commissioning and qualification of facilities, equipment and utilities projects in the biopharmaceuticals industry.

3. Examine the current status of Quality Risk Management implementation in C&Q in the biopharmaceuticals industry.
4. Examine critically the outcome of the early examples of implementation of risk-based C&Q to evaluate the benefits and identify barriers to successful execution
5. Explore the organisational and operational changes required by stakeholders in order to implement risk-based C&Q.
6. Formulate recommendations regarding the implementation of risk-based C&Q.

1.4 Value of this Research

There is a need now in the biopharmaceuticals industry to embrace fully the guidance on Quality Risk Management and on a science and risk based approach to C&Q. Being a highly regulated industry, the biopharmaceuticals industry is sensitive to risk and always cautious about changes to its methods of operation.

In addition, as the move towards a science and risk-based approach to qualification is very recent and is still in its infancy in many pharmaceutical companies, it is reasonable to assume that the level of knowledge and understanding of these concepts among industry professionals varies widely within the industry.

This dissertation will address gaps in the knowledge and understanding that C&Q stakeholders might have by outlining the differences between the BG5 approach and the science and risk-based approach. This research will contribute to the development of risk-based C&Q in the industry by comparing different Quality Risk Management approaches adopted in the industry in order to determine if common difficulties/ benefits can be identified.

2.0 LITERATURE REVIEW

The literature review will focus on the learning objectives outlined in section 1.3. Sections 2.1, 2.2 and 2.3 will follow objective 1 and will trace the development of traditional C&Q practices over the last 25 years. In line with objective 2, sections 2.4 and 2.5 will analyse the basic regulatory initiatives which describes the Quality Risk Management process that the regulators expect the biopharmaceuticals industry to implement. Also following objective 2, section 2.6 will analyse the risk-based C&Q industry guidance which has arisen from the regulatory initiatives. Section 2.7 will address objective 3, which is to examine the current status of Quality Risk Management implementation in C&Q in the biopharmaceuticals industry. Sections 2.8 and 2.9 will focus on evaluating the benefits and the difficulties of facing risk-based C&Q, in line with objective 4, while section 2.10 will discuss the updated regulatory guidance on risk-based C&Q. Section 2.11, 2.12 and 2.13 will focus on objective 5 and will evaluate critically the latest industry guidance documents to explore the organisational and operational changes required in the biopharmaceuticals industry in order to implement risk-based C&Q. In particular these sections will examine the changing roles and responsibilities of the stakeholders and the main C&Q supporting processes.

2.1 The Beginning of Modern C&Q: FDA Process Validation Guideline 1987

In 1987 the FDA issued its first guidance on process validation (FDA, 1987). Process Validation had previously been deemed a requirement of Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals in 21 CFR Parts 210 and 211 and many companies had requested guidance from the FDA in terms of their expectations of what companies needed to do to ensure compliance. Modern day C&Q practices really began with this document. Process validation was defined as:

"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics" (FDA, 1987).

This document introduces a number of basic principles of Quality Assurance. They are that:

"(1) Quality, safety, and effectiveness must be designed and built into the product;

(2) Quality cannot be inspected or tested into the finished product

(3) Each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specifications

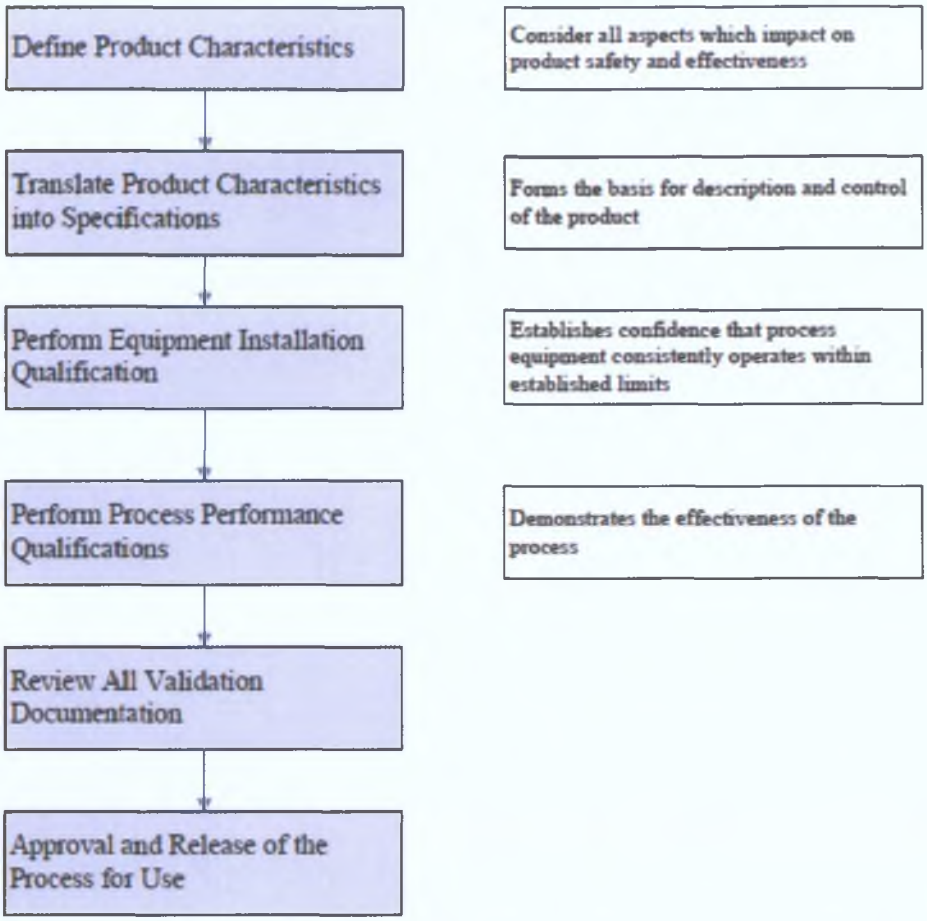
(FDA, 1987, p.3)

Under the process validation guideline, a manufacturer was expected to "evaluate all factors that affect product quality" in order that the product could be "carefully defined in terms of its characteristics" (FDA, 1987, p.7).
Furthermore, the guideline stated that "all aspects of the product which impact on safety and effectiveness should be considered" (FDA, 1987, p.7).

This document proposed a qualification framework of installation qualification (IQ) followed by process performance qualification. The guidance was very much system and equipment based, calling for studies to "establish confidence that the process equipment and ancillary systems are capable of consistently operating within established limits and tolerances" (FDA, 1987, p.7). This statement sets out the expectation that equipment will operate according to specifications. There is no explicit link made to the protection of the quality of the product and, by extension, to the safety of the patient. Figure 2.1 summarises the validation process as outlined in the 1987 Process Validation Guideline.

The concept of risk management was not introduced in this document but a firm link was made between process conditions and the qualification effort by calling for equipment to be "evaluated and tested to verify that it is capable of operating satisfactorily within the operating limits required by the process" (FDA, 1987).

Figure 2.1: Validation of Equipment Process Flow Proposed by FDA Process Validation Guideline 1987



2.2 The First Risk Assessment Process in C&Q – ISPE Baseline Guide 5, 2001

In 2001, the ISPE, in its Baseline Guide 5, highlighted the trend towards "increases in the costs of new facilities" (ISPE, 2001) in the foreword. They stated that validation had become a significant area for concern particularly the trend to "validate back to source utilities". They determined that "the absence of a consistent and widely accepted interpretation of some regulatory requirements" was one of the causes of the problem and the effect of this was

leading to "increased costs, longer lead times and delays in bringing new products to market" (ISPE, 2001).

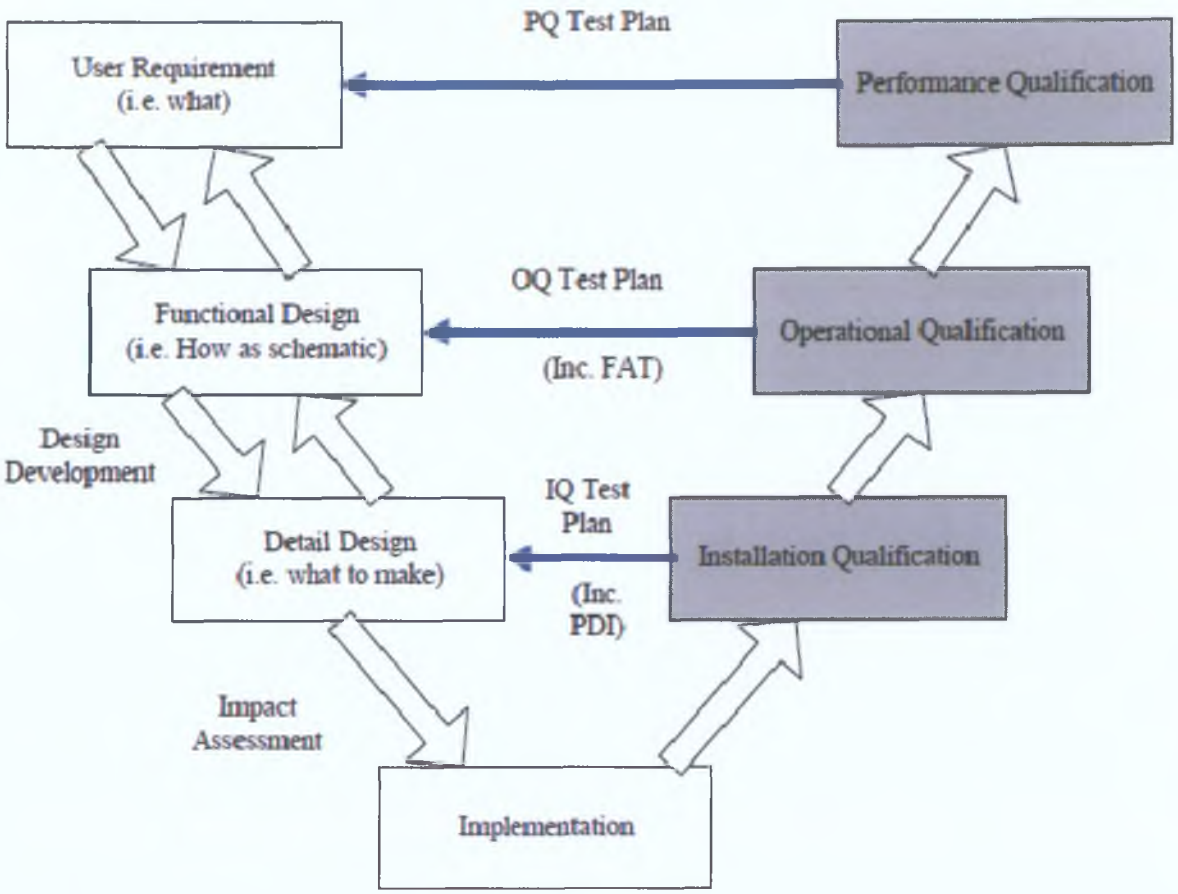
From these statements it can be understood that in the ten years or so following the Process Validation Guideline that concerns were mounting in the industry regarding the cost and schedule impact of commissioning and qualification. In response, the ISPE proposed a clear methodology for commissioning and qualifying facilities, utilities and equipment regulated by the FDA. This model was called the V-model and it is shown in Figure 2.2. The basic philosophy espoused by Baseline Guide 5 was that:

1. "Good Engineering Practice (GEP) makes a significant contribution to meeting the regulatory demands of the pharmaceuticals industry.
2. Where engineering systems may have a Direct Impact on product quality, supplementary Qualification Practices (in addition to GEP and Commissioning) are required to fully address pharmaceutical industry demands.
3. The baseline approach is to restrict the application of Qualification Practices to "Direct Impact" Systems and build on the contribution of GEP and Commissioning.
4. Good Engineering Practice is a satisfactory approach for "Indirect" or "No Impact" Systems" (ISPE, 2001).

The additional qualification practices that were referred to in points 2 and 3 were furthermore listed as "Impact Assessment, Qualification Rationales, active participation of QA, Enhanced Documentation and Document Management, greater End-user participation and additional tests and checks" (ISPE, 2001).

The V-model envisaged a well-structured methodology of Commissioning and Qualification in which, following an Enhanced design Review (EDR) of a system design, IQ would be used to verify the construction and installation, OQ would be used to verify the functional requirements of a system and PQ would be used to verify the User requirements.

Figure 2.2: ISPE Baseline Guide 5 V-Model for C&Q



(ISPE, 2001)

The Impact Assessment of Baseline Guide 5 was the first Risk Assessment step to be formally introduced to C&Q practices. The Impact Assessment process proposed by the ISPE involved two levels of assessment, a system level impact assessment (SLIA) and a component level impact assessment (CLIA). The ISPE defined a system as "an organisation of engineering components that have a defined operational function" (ISPE, 2001). The work flow for an SLIA is outlined in Figure 2.2. The first step of the SLIA process was to identify the number and scope of different systems. The second step was to ascertain if a system could be classed as "Direct Impact", "Indirect Impact" or "No Impact". This was

done by asking a series of questions about each identified system to determine if the criteria for direct impact applied. These questions are outlined in Table 1.

Table 2.1: ISPE Baseline Guide 5 SLIA Direct Impact Criteria

Number	Question
1	Does the system come in direct contact with the product?
2	Does the system provide an excipient or produce an ingredient or solvent? (e.g. WFI)
3	Is the system used in cleaning/sterilizing? (e.g. clean steam)
4	Does the system preserve product status? (e.g. nitrogen)
5	Does the system produce data used to accept or reject product?
6	Is the system a process control system (eg PLC/DCS) that may control or manipulate a process in such a way to affect product quality without independent verification of the control system performance?

By its nature this type of risk assessment was fundamentally focused on systems and equipment. The focus of the questions is more related to the function of the equipment and does not make any explicit links to the quality of the product and the safety of the patient. A typical SLIA tool, as depicted in figure 2.3 can demonstrate the extent to which the tool is system based. In the figure shown, all questions relate to the system and equipment only and there is no mention of product quality.

Figure 2.3: Typical Baseline Guide 5 SLIA Tool

System Identification and Location					System Impact Assessment						SIA		
SYSTEM NUMBER	SYSTEM NAME	SYSTEM EQUIPMENT	SYSTEM EQUIPMENT TAG NUMBERS	Area	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	No Impact	Indirect Impact	Direct Impact

In the second part of the impact assessment, the CLIA, each component within the "Direct Impact" or "Indirect Impact" systems were assessed for criticality. Components were assessed against criteria laid out in table 2.

Table 2.2: ISPE Baseline Guide 5 CLIA Direct Impact Criteria

Number	Question
1	The component is used to demonstrate compliance with the registered process.
2	Operation of the component has a direct effect on product quality.
3	Failure of the component has a direct effect on product quality.
4	Information from the component is recorded as part of the batch record.
5	The component is in direct product contact.
6	The component controls critical process elements that may affect product quality, without independent verification of the control system performance
7	The component is used to create or preserve a critical status of a system.

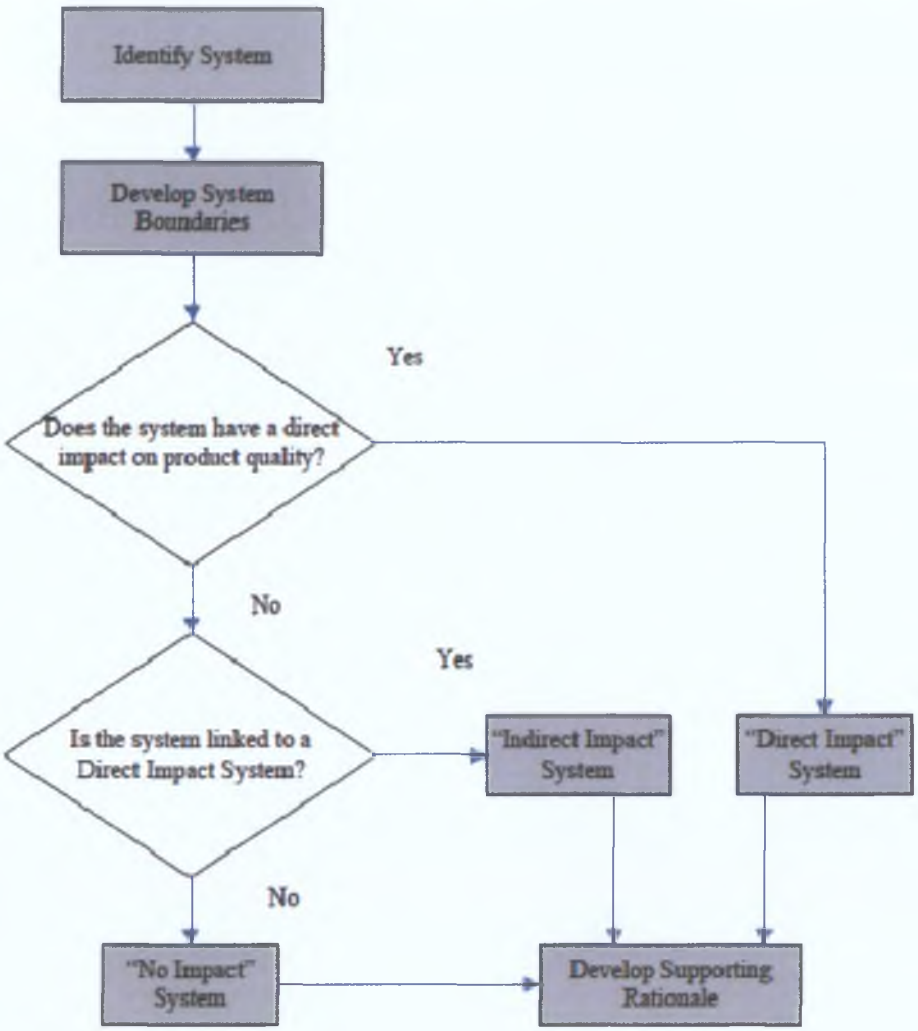
It was foreseen that the participants in the impact assessment process would typically include:

- User Representative
- Process Experts
- Relevant Engineering Disciplines
- Validation Manager
- Quality Assurance Representative

It was proposed to engage in a practice called "Design for Impact" in order to reduce the number of Direct Impact systems. It was suggested that this would reduce the number of systems subject to Qualification Practices, "allowing appropriate focus on the components presenting a risk to product quality" (ISPE, 2001).

In the years since Baseline Guide 5 has been published, it has become the standard for commissioning and qualification practices. EU guidelines Volume 4, Annex 15, also propose the framework of IQ, OQ and PQ (EMA, 2001). These practices have become the general standard in the industry since 2001.

Figure 2.4: ISPE Baseline Guide 5 System Level Impact Assessment Work Flow



(ISPE, 2001)

2.3 A Paradigm Shift – The Risk and Science-Based Approach

In August 2002 the FDA announced a significant new initiative, "Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century" (FDA, 2004). The aim of the new initiative was to" enhance and modernise the regulation of pharmaceutical manufacturing and product quality — to bring a 21st century focus to this critical FDA responsibility" (FDA, 2004, p.4). The FDA recognised that regulatory hurdles had prevented manufacturers from changing their manufacturing processes and they held out the prospect of a regulatory framework that would accommodate process change to support continuous process improvement" (FDA, 2004, p.10).

The report was published in September 2004 and in it the FDA said that their "assessment helped (them) create a new framework for the regulatory oversight of manufacturing quality that is based on quality systems and risk management approaches". In this report, the FDA highlighted that, in the past, the FDA "exercised extensive control over virtually every aspect of the manufacturing process" (FDA, 2004, p.10). The FDA referred to "significant advances in manufacturing science, quality management systems and risk management" that had taken place in recent years. It was the goal of this initiative to encourage pharmaceutical manufacturers to make use of these tools in order "to facilitate the implementation of robust manufacturing processes that reliably produce pharmaceuticals of high quality and that accommodate process change to support continuous process improvement" (FDA, 2004, p.10).

The FDA stated that, beginning in 2004; it would "begin using a risk-based approach for prioritising domestic manufacturing site inspections for certain human pharmaceuticals". The burden of inspections would be reduced for firms that FDA "determines have acquired sufficient process understanding and have succeeded in implementing effective quality systems approaches" (FDA, 2004, p.11). They also stated that the new risk-based quality assessment system, which would replace the CMC review system, "would focus on critical pharmaceutical quality attributes and their relevance to safety and efficacy" (FDA, 2004).

These statements hold much significance for the biopharmaceutical industry. As the FDA regulates product quality, it is now telling the biopharmaceuticals industry that it will assess "the degree to which an application reflects a manufacturer's understanding of manufacturing process, process control, and quality systems" (FDA, 2004, p.11) and that it would do this using a risk-based quality assessment system. The FDA also state that: "as a pillar of the initiative (and guiding principle), the Agency must ensure that science-based policies and standards form the foundation upon which product quality regulation is based" (FDA, 2004, p.8).

For the biopharmaceuticals industry this marks a new departure. In the future, product quality regulation would now be guided by the following principles:

- A Risk-Based Approach.
- A Science-Based Approach.
- A Quality Systems Approach.

The CGMP initiative also recognised that there was a requirement for International Regulatory partners to co-operate to address the issues surrounding Quality Systems and Quality Risk Management. Arising out of this initiative, ICH established working groups to develop a pharmaceutical quality system based on an integrated approach to risk management and science. The three documents that would be produced would be ICH Q8, Pharmaceutical Development, ICH Q9, Quality Risk Management and ICH Q10, Pharmaceutical Quality System. These documents would provide the biopharmaceuticals industry with a consistent, harmonized, industry-wide framework for the new science and risk-based approach to product quality assurance.

2.4 Pharmaceutical Development and Quality Risk Management; ICH Q8 and ICH Q9.

In November 2005, the ICH issued ICH Q9, Quality Risk Management. One of the primary objectives of this dissertation is to describe the Quality Risk Management Process as it applies to commissioning and qualification of facilities, equipment and utilities projects in the Biopharmaceuticals industry. ICH Q9 is the basis document for Quality Risk management in the Biopharmaceutical industry. ICH Q9 defines Quality Risk Management

as: "a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle" (ICH, 2005, p.2).

The first paragraph of ICH Q9 outlines the current status of Quality Risk Management at the time of issue:

> "Although there are some examples of the use of quality risk management in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system" (ICH, 2005, p.1).

In this statement ICH Q9 also makes the link between Quality Risk Management and Quality Systems. This is an important link as, while ICH Q9 sets out the thinking on Quality Risk Management, ICH Q8 and ICH Q10 outline the type of Quality System that is expected to be in place in a biopharmaceutical company in order to execute a comprehensive Quality Risk Management programme.

ICH Q9 offers a more all-encompassing and far-reaching vision of what is required in order to maintain product quality:

> 'The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies" (ICH, 2005, p.1).

This statement highlights the importance of the drug quality attributes that have been developed in clinical studies. In turn, ICH Q8 describes how this knowledge might be arrived at. ICH Q8 proposes a framework for Pharmaceutical Development, based on Quality by Design, such that the Critical Quality Attributes (CQAs), the Critical Process Parameters (CPPs) and process control strategy are identified. ICH Q8 is based on the core principle of Quality by Design (QbD) which is that quality cannot be tested into a product, it must be built in by design. ICH Q8 and ICH Q9 are complementary guidance documents, ICH Q8 providing the guidance regarding the development of critical quality attributes, critical

process parameters and product and process information and ICH Q9 providing guidance on how to manage the risk to the product quality.

The benefits of Quality Risk Management, according to ICH Q9, are that:

- "An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing.
- Use of quality risk management can improve the decision making if a quality problem arises.
- Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight" (ICH, 2005, p.1).

ICH Q9 also highlights that one of the major difficulties of quality risk management is the achievement of a shared understanding of QRM with the diversity of opinions of the different stakeholders which might include patients, medical practitioners, government and industry. Furthermore, it is proposed that the participants in a QRM process would come from many different disciplines including the quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical departments (ICH, 2005, p.3).

It is interesting to contrast this list of participants with the list presented in the earlier discussion regarding Impact Assessments in Section 2.2. This implies that the QRM process is a much more involved and far-reaching process than the Impact Assessment process and demands more resources at an earlier stage of a project than would normally be committed under Baseline Guide 5 C&Q approach.

ICH Q9 sets out the two primary principles of quality risk management as follows:

1. "The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient" and
2. "The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk" (ICH, 2005, p.2)

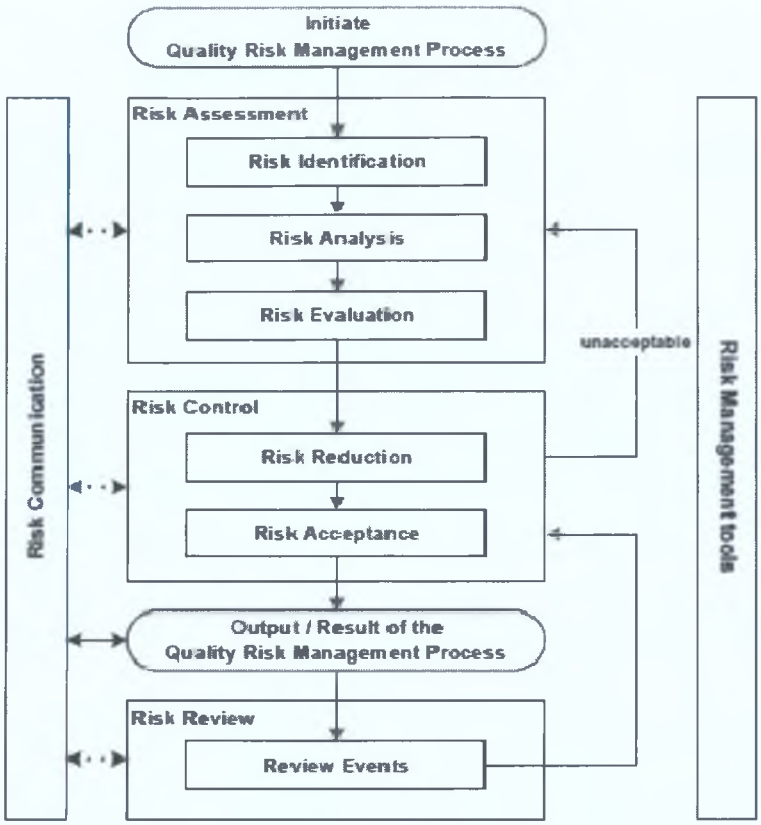
These principles reinforce the link between quality risk management and information such as CQAs and CPPs generated through clinical studies.

Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. The general QRM methodology is set out in Figure 5. ICH Q9 proposes that in carrying out the risk assessment step the following three questions can be asked:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Question 1 helps to identify the risks, while questions 2 and 3 are necessary in order to analyse the risk before the risk can be evaluated. The output from the risk assessment process is an estimate, either qualitative or quantitative of the level of risk. The next step is risk control where decisions are made to either reduce or accept the risk. Risk communication may be ongoing throughout the QRM process with other stakeholders and it is recommended that risk review is carried out on an ongoing basis throughout the entire quality management process.

Figure 2.5: Overview of a Typical Quality Risk Management Process



(ICH, 2005)

Numerous recognised risk management tools are proposed in the document including:

- Basic risk management facilitation methods (flowcharts, check sheets etc.);
- Failure Mode Effects Analysis (FMEA);
- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools.

The document states that no one set of tools is applicable to every situation and this dissertation will look at current practice in the biopharmaceutical industry and attempt to

establish the nature of Quality Risk Management programmes in the Biopharmaceuticals industry.

2.5 Quality Risk Management within a Pharmaceutical Quality System – ICH Q10

ICH Q10, issued in 2008, is a complementary guidance document to ICH Q8 and Q9 and defines an entire quality management system for the pharmaceutical industry. It is intended to be implemented throughout the different stages of a product lifecycle. The different stages of a product lifecycle are identified as follows:

1. Pharmaceutical Development
2. Technology Transfer
3. Commercial Manufacturing
4. Product Discontinuation

Provision of facilities, utilities, and equipment, and therefore the commissioning and qualification of same, is defined as a technical activity within the commercial manufacturing phase of the lifecycle. ICH Q10 states that: "Quality risk management is integral to an effective pharmaceutical quality system" (ICH, 2008, p.3). In this researcher's opinion, effective performance of the Risk Control, Risk Review and Risk Communication steps of ICH Q9 are only possible if an effective pharmaceutical quality system, as defined in this guidance, is in place. Without an effective pharmaceutical quality system, it is difficult to see who exactly will finally accept the risk (Risk Acceptance), who will communicate the output of the risk management process and to whom (Risk Communication), and who will review the risk (Risk Review) at periodic intervals as "the body of knowledge is continually expanded" (ICH, 2008, p.7).

It is clear also that ICH Q10 places the responsibility on senior management to ensure that the pharmaceutical quality system, of which QRM is such an integral part, is implemented: "Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives, and that roles, responsibilities,

and authorities are defined, communicated and implemented throughout the company" (ICH, 2008, p.4).

ICH Q10 proposes the establishment of a Quality Manual detailing the quality policy, the scope of the pharmaceutical quality system, details of the quality systems processes and management responsibilities. Management, in particular, are tasked with helping to design and implement the system, ensuring an effective communication process exists, defining individual and collective roles and responsibilities, conducting appropriate reviews and committing appropriate resources.

In particular ICH Q10 highlights four elements of a pharmaceutical quality system:

- "Process performance and product quality monitoring system;
- Corrective action and preventive action (CAPA) system;
- Change management system;
- Management review of process performance and product quality."

(ICH, 2008, pp.7,8).

In terms of the first of these elements, the process performance and product quality monitoring system, ICH Q10 proposes the use of quality risk management to establish "facility and equipment operating conditions" (ICH, 2008, p.8). Under the third element, the change management system, it also states that quality risk management should be used to evaluate proposed changes.

The significance of these statements, in the researcher's opinion is that ICH Q10 recommends that quality risk management should be used for qualification of equipment and for evaluation of changes, as part of an effective pharmaceutical quality system.

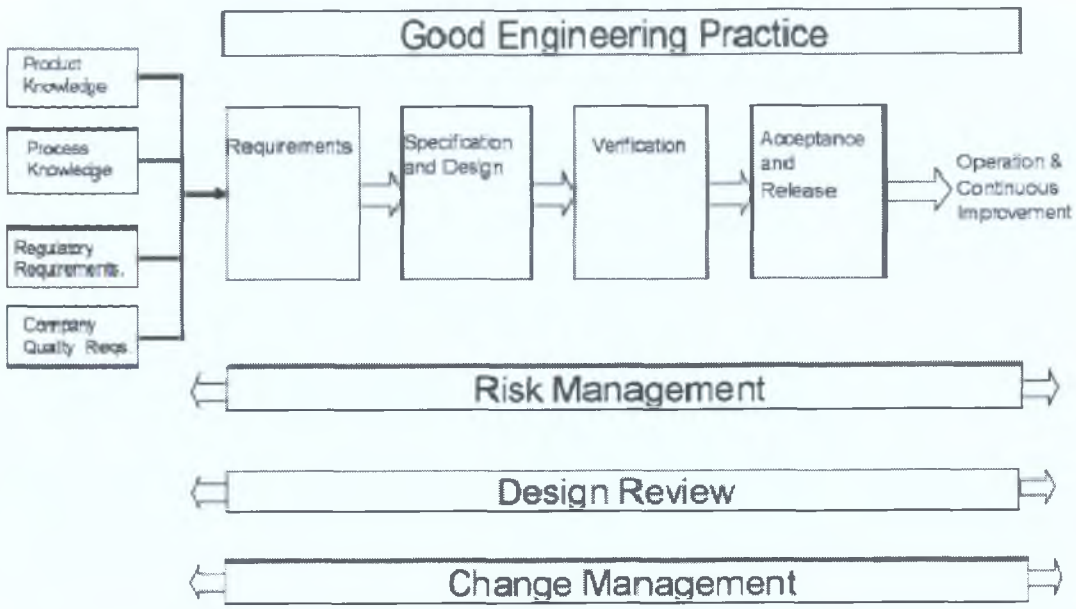
2.6 Commissioning and Qualification Becomes Verification – ASTM E2500-07

In 2007 ASTM issued its Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment (ASTM, 2007). This document represented a major leap forward in terms of the utilisation of Quality Risk Management in C&Q and in the evolution of C&Q practices as a whole. It is very strongly aligned with ICH Q8, ICH Q9 and Pharmaceutical CGMPs for the 21st Century. In fact these are the only three documents that it references.

ASTM E-2500 defines a new term, "verification", in place of commissioning and qualification (ASTM, 2007, p.1). It defines verification as:
"A systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other" (ASTM, 2007, pp.1,2).

The basic process flow for verification, outlined in figure 2.6, consists of (a) requirements definition, (b) specification and design, (c) verification and (d) acceptance and release. Underlying this process are three supporting processes: risk management, design review and change management with good engineering practice applied throughout. The guide recommends following the science-based approach of ICH Q8 in order to develop requirements and the risk-management approach of ICH Q9 in order to implement Quality Risk Management.

Figure 2.6: The ASTM E2500-07 Verification Process Flow



(ASTM, 2007)

In addition the ASTM guide applies the following key concepts (ASTM, 2007, p.2):

- Risk-based Approach
- Science-based Approach
- Critical Aspects of Manufacturing Systems
- Quality by Design
- Good Engineering Practice
- Subject Matter Expert
- Use of Vendor Documentation
- Continuous Process Improvement

After ten years of implementation of the Baseline Guide 5 V-model, and broad acceptance of it in the industry, E2500-07 proposes "a markedly different process for assuring that equipment, facilities and manufacturing systems generally are fit for use" (IMB, 2010). It proposes a new methodology called verification and it is underpinned by Quality Risk Management. As the IMB have noted: "E2500-07 relies heavily on effective Quality Risk Management" (IMB, 2010, p.14).

Good Engineering Practice is one of the key concepts of ASTM E2500-07 and is defined as "those established engineering methods and standards that are applied throughout the life cycle to deliver appropriate and effective solutions" (ASTM, 2007, p.2)

The ISPE Good Practice Guide states that Good Engineering Practice is "an overall and holistic life cycle approach to engineering that spans the complete lifecycle of a facility or system, from design to decommissioning" (ISPE, 2011, p.56). It further recommends that an Engineering Quality system be used to "provide a systematic engineering structure to define, develop and implement efficient and streamlined engineering processes" (ISPE, 2011, p.55).

2.7 Quality Risk Management in Industry post ASTM E2500-07

The third and fourth research objectives outlined in section 1.3 of this report are as follows:

3. Examine the current status of Quality Risk Management implementation in C&Q in the biopharmaceuticals industry.
4. Examine critically the outcome of the early examples of implementation of risk-based C&Q to evaluate the benefits and identify barriers to successful execution

One of the most valuable resources that the research uncovered is the proceedings of relevant ISPE conferences held since 2007. This section will use the findings reported at the following conferences in order to obtain a full picture of how industry implementation of the new risk-based approach is proceeding:

- Barcelona 2008
- Manchester 2008
- Strasbourg 2009
- San Diego 2009
- Cork 2010
- Orlando 2010
- Dallas 2011

2.7.1 Quality Risk Management Tools in Industry

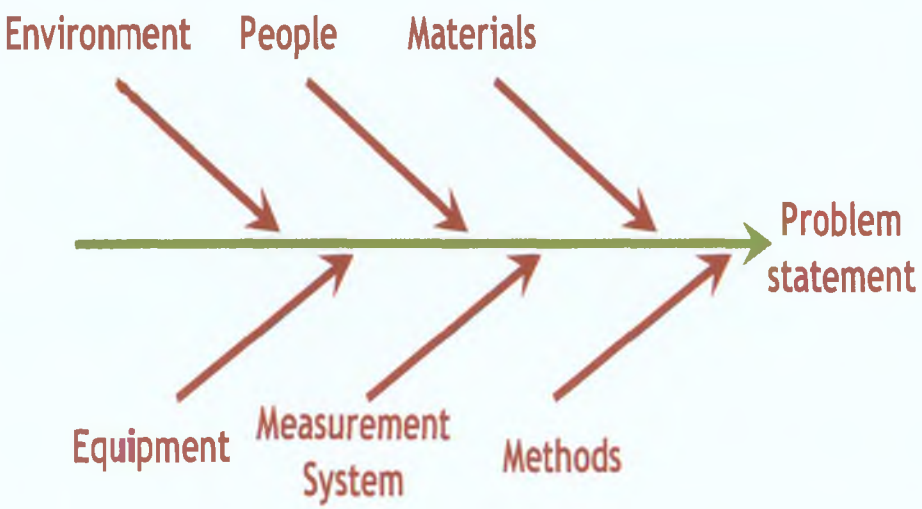
ICH Q9 lists a number of modern risk management tools that could be considered useful in the biopharmaceuticals industry. These are listed in Section 2.4 of this report. The point is also made that "no one tool or set of tools is applicable to every situation" (ICH, 2005, p.11). However, when discussing the tools further, Failure Modes and Effects Analysis (FMEA) is highlighted as having potential uses in equipment and facility design.

Under ISO guidelines the following terminology is used when conducting risk assessments:

- Harm: Damage to health, including the damage that can occur from loss of product quality or availability.
- Hazard: The potential source of harm (ISO/IEC Guide 51).
- Risk: The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).
- Severity: A measure of the possible consequences of a hazard.

In the authors own experience basic risk management methods such as cause and effect diagrams, as shown in figure 2.7, can be helpful in identifying risks. In terms of ICH Q9, this can also fulfill the first step of risk assessment which is risk identification.

Figure 2.7: Cause and Effect Diagram (Ishikawa/ Fish bone)



The output from a risk identification process like the fishbone diagram in Figure 7 needs to be couple with another tool in order to complete the risk assessment process. FMEA is commonly used in industry for risk assessments and the typical layout of the tool is represented in 2.8. FMEA involves identifying firstly the failure modes for the risks which corresponds to the risk analysis step in ICH Q9. The second step is to assign rankings to the severity of an occurrence(S), the probability of an occurrence (P) and the detectability (D) of an occurrence. The risk is the combination of the three rankings and this risk protection number (RPN) is then used to evaluate the risk and can carry out the risk evaluation step of ICH Q9. If the risk is too high, risk mitigation measures can then be proposed in order to reduce the risk and the analysis run again. If the risk is reduced sufficiently it can then be accepted. This fulfils the risk reduction and the risk acceptance steps of ICH Q9.

Figure 2.8: Standard FMEA Template

System	Identified Risks	Effects of Failure	Causes of Failure	Risk Analysis						Risk Mitigation / Action	Revised Risk	Action Item / Risk Mitigation Confirmed
				Severity (1-5)	Existing Risk Controls	Probability of Occurrence (1-5)	Likelihood of Detection (1-5)	Risk Priority Number	Risk Rating			

E2500-07 states that "product and process information, as it relates to product quality and patient safety, should be used as the basis for making science- and risk-based decisions" (ASTM, 2007, p.2). It identifies example of product and process information as: "critical quality attributes (CQAs), critical process parameters (CPPs), process control strategy information, and prior production experience" (ASTM, 2007, p.2).

Furthermore, E2500-07 identifies critical aspects of manufacturing systems as:

"Functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety" (ASTM, 2007, p.2).

It also states that "verification activities should focus on these aspects of manufacturing systems" and that they should be "identified and documented based on scientific product and process understanding" (ASTM, 2007, p.2).
Finally E2500-07 states that, "based on risk assessments, appropriate controls and verification techniques should be selected to manage risk to an acceptable level, focusing on those relating to the critical aspects of the manufacturing system" (ASTM, 2007, p.4).

Standard risk management tools that are used in other industries such as the automotive industry are not equipped to deal with these specific requirements. Deconinck and Dollard outlined an approach using an FMEA modified for ASTM E2500-07 QRM application (DeConinck & Dollard, 2010). A broad summary of this approach is outlined in Figure 2.9.

Figure 2.9: Modified FMEA for use in ASTM E2500-07 QRM process

Process step	Hazard	CQA	CPP	Failure Mode	Risk Analysis						Critical Aspect (subject to Verification)	Risk Mitigation Confirmed
					Severity Ranking	Probability of Occurrence Ranking	Control and Detection Mechanisms	Risk Class	Detectability	Risk Priority		

(DeConinck & Dollard, 2010)

The starting point for this procedure is the process step itself along with process and product information such as CQAs and CPPs. Hazards with impact on CQAs and CPPs are identified and risk assessed. Hazards with unacceptably high risk ratings can be reduced by risk mitigation measures. Any risk mitigation measure is by definition a critical aspect and thus the critical aspects which form the focus of the verification programme are identified.

An important aspect of an FMEA-based tool is the risk scoring approach. DeConinck, Lucchesci and Van der Steen have adopted an approach based on the method outlined in GAMP (Van der Steen, 2009), (DeConinck & Dollard, 2010), (Lucchesci, 2010). In the GAMP approach, severity of impact on patient safety and product quality is plotted against

the likelihood that a fault will occur, giving a risk class. Risk class is then plotted against the likelihood that the fault will be detected before harm occurs, giving a Risk Priority.

Figure 2.10: Risk Class Scoring Definition

Risk Class		Probability		
		L	M	H
Severity	H	2	1	1
	M	3	2	1
	L	3	3	2

(De Coninck, 2010)

In the case of probability, L means an occurrence of once every 100 batches, M means once every 10 – 100 batches and H means once every 1-10 batches. In the case of severity, L means negligible effect on a patient, M means a minor effect on a patient and H means a serious or life threatening effect on a patient.

Figure 2.11: Risk Priority Scoring Definition

Risk Priority		Detection		
		L	M	H
Risk Class	1	2	1	1
	2	3	2	1
	3	3	3	2

(De Coninck, 2010)

In terms of detection, H means the problem is detected during the process, M means that the the problem can be detected within the site quality system and L means that the problem is detected outside the site quality system. Finally the risk priority is assigned as follows:

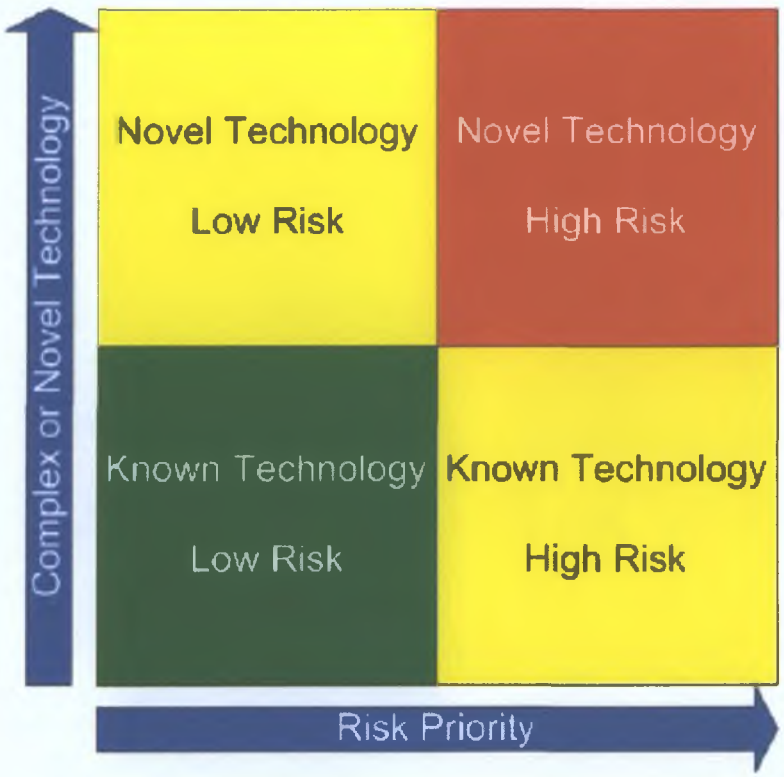
- L: Acceptable without further examination
- M: Examine more qualitatively to assess if further mitigation is required
- H: Unacceptable and in need of further mitigation

Fault Tree Analysis is recommended for "integrated systems analysis" which forces the user to "think across system boundaries" (Howard, 2010). Howard also suggests that HACCP is also suggested as a tool that can be used when examining physical, chemical and biological

hazards to the process (Howard, 2009). It is stated however that the focus of this tool is mainly on the lifecycle of the product and not on the manufacturing process.

Howard also proposes a Boston Matrix as a useful tool in order to "drive focus to area of most need" (Howard, 2010). The basic premise of the Boston Matrix as applied to FAT planning is outlined in Figure 2.12. This approach helps to focus the FAT effort on the most critical areas.

Figure 2.12: Example of Boston Matrix applied to FAT planning.



(Howard, 2010)

Browne and Fischer (Browne & Fischer, 2010) explained how a preliminary hazard analysis tool can be used in the industry. A requirements document is prepared which identifies CQAs, CPPs and their corresponding process and product requirements. During a design review, these requirements are then analysed by the risk assessment team to determine the particular manufacturing system critical aspect, the verification test strategy and the verification test acceptance criteria. The authors state that further risk assessment tools may be applied to particular critical aspects (Browne & Fischer, 2010).

This approach allows for:

- Identification of Critical Aspects
- Identification of intended design and control strategy for the Critical Aspects
- Identification of verification test strategy for the Critical Aspects
- Identification of acceptance criteria for Critical Aspect testing.

An outline of the risk assessment tool used in this example is presented in figure 2.13.

Figure 2.13: Risk Assessment Tool used in QRM by Browne and Fischer

Requirements Document				Design Review Document		
Risk Identification and Assessment				Risk Control and Mitigation		
Critical Aspect Identifier	CQA	CPP	Product Process Requirement	Design Solution	Verification Test Strategy	Verification Test Acceptance criteria

(Browne & Fischer, 2010)

ICH Q9 states that "it is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used" (ICH, 2005, p.11). The literature demonstrates that many different risk assessment tools can be of use in the biopharmaceutical industry, depending on the application.

Murray and Reich studied Quality Risk Management Tool selection (Murray & Reich, 2011). They stated that "the capability to manage quality risks may suffer if we apply a one-size-fits-all approach" (Murray & Reich, 2011, p.1). They state that in order for QRM to be "meaningful, effective and efficient", the tools should be "carefully chosen to fit the problem statement and the intent of the risk assessment" (Murray & Reich, 2011, p.1). They point out that poorly chosen QRM tools may lead to several problems:

- Risks may go unaddressed
- Significant risks may be underrated while insignificant risks may be overrated
- Strengths in risk control may be underestimated, while weaknesses in risk control may be overestimated
- Risk assessments may be overly complex and lengthy

- Misuse of QRM tools may be cited as non-conformance and thus the exercise may be called into question by stakeholders

In selecting a QRM tool, the authors propose that the risk management facilitator should first focus the team on:

- Defining a preliminary risk problem statement
- Defining the scope and boundaries of the risk assessment
- Identifying the available data to support the assessment
- Undergoing a preliminary risk identification exercise

They state that these prerequisites are "essential for the process of QRM tool selection" (Murray & Reich, 2011, p.3). In order to assist in the process of tool selection, the authors provide a matrix which allows each tool to be analysed against the main tool selection considerations. This matrix is outlined in Figure 2.14. In this case, "No" does not mean disqualification but simple reduced effectiveness

Figure 2.14: QRM Tool Selection Analysis Matrix

Considerations	FMEA	FTA	Fishbone	HACCP	HAZOP	PHA	RR&F
System knowledge is limited (early lifecycle).	No	Yes	Yes	No	Yes	Yes	Yes
System knowledge is advanced (later lifecycle) .	Yes	Yes	Yes	Yes	Yes	No	Yes
Problem statement is simple.	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Problem statement is complex.	Yes	Yes	No	Yes	Yes	No	No
Risk ranking is desired	Yes	No	No	No	No	Yes	Yes
Risk detection capability is limited.	No	Yes	Yes	Yes	Maybe	Maybe	Maybe
Risk data is qualitative in nature.	No	Yes	Yes	No	Yes	Yes	Yes
Risk data is quantitative in nature.	Yes	Yes	No	Yes	Yes	Yes	Yes
Demonstration of effectiveness of risk control is required.	Yes	No	No	Yes	No	No	No
Risk identification is a challenge, structured brainstorming is required.	No	Yes	Yes	No	Yes	No	No

(Murray & Reich, 2011)

It can be seen that, depending on the circumstances, there are many tools available in order to carry out an effective QRM programme. As Murray and Reich pointed out:
"The full benefits of QRM are consistently realised only when the best tools are selected for the job" (Murray & Reich, 2011, p.6). Instead of standardising the risk management effort around a limited set of tools, it is better instead to standardise on a flexible and well-considered approach to QRM tool selection.

2.7.2 Difficulties with Risk Assessment Tools

Calnan (Calnan, 2011) has highlighted the difficulties posed by human heuristics in risk assessment processes. Heuristics are cognitive behaviours which come into play when humans make judgements in the presence of uncertainty. In the case of QRM, Calnan states that 'awareness of the potential adverse influences of human heuristics is key to implementing QRM tools successfully" (Calnan, 2011).

The three heuristics highlighted by Calnan are:

- Heuristic of anchoring and adjustment
- Heuristic of availability
- Heuristic of representativeness

When the heuristic of anchoring and adjustment is in operation, people's judgement can be heavily influenced by the first approximation of the value or quantity that they hear, termed an "anchor" (Calnan, 2011).

Heuristic of availability affects how people estimate the probability of an event occurring. A persons judgement of the probability of an event can be determined by the ease with which they can imagine the event occurring. If a person can easily imagine an event occurring, they may overestimate its frequency but if it is difficult for that person to imagine, then they may underestimate its frequency (Calnan, 2011).

The heuristic of representativeness can lead people to pay too much attention to specific details and pay insufficient attention to important background information (Calnan, 2011).

2.7.3 Difficulties with the Quality Risk Management Process

Some practical problems with the application of QRM to C&Q have been reported in the literature. Brunelle highlighted that GEPs and Risk Assessments were not well established and understood (Brunelle, 2011). GEP was also highlighted as a key consideration by DeConinck, who also highlighted construction quality procedures as a critical element for project success (De Coninck, 2010).

Browne and Fischer highlighted the key lessons learned from their experience of QRM as being:

1. "Earlier involvement of Quality Unit and Technical Services/Development groups was required in order to define the product/process requirements.
2. GEP needs to be well established and understood by key stakeholders.
3. Risk Management principles need to be well understood and appropriately applied."

(Browne & Fischer, 2010)

A key challenge also highlighted in that project was the changing roles and responsibilities of the stakeholders (Browne & Fischer, 2010).
Slock highlighted the main challenges as being the requirement for greater understanding of product and process at an earlier stage of the project and the increased reliance on GEP (Wrigley & Slock, 2009).

Dolgin pointed out the need for management support and highlighted that the change in responsibility seemed particularly difficult for the Quality Unit while also stating that new documentation requirements need to be communicated and agreed with suppliers and vendors (Dolgin, 2011).

O' Donnell identified poorly structured brainstorming sessions which were susceptible to subjectivity and uncertainty as a barrier to successful implementation (O'Donnell, 2007, p.213)

These problems point out the need for a holistic approach to QRM with C&Q, encompassing supporting practices such as GEP. Two other recurring themes, among the difficulties reported, are the problems with the risk assessment process itself, in terms of lack of training or participation and the difficulties in bringing about a culture change within the Quality Unit.

2.7.4 A Regulatory Perspective on the QRM Process

From a regulatory point of view O'Neill (O'Neill, 2009) made a clear distinction between risk management and risk assessment, explaining that while risk assessment is about individual documents, risk management concerns a holistic process to managing risk. He highlights the importance of "true experts in the risk management process" (O'Neill, 2009) and expects that as the process is new that both industry and regulators can expect to have bad experiences.

Kevin O'Donnell, of the Irish Medicines Board, highlights other issues from a regulatory point of view with QRM (O'Donnell, 2010). He sees the current problems with QRM as being:

- "Inadequate assessment of the value of current controls in risk mitigation before risks is rated using RPN-type approaches.
- Poor linking of the outputs of QRM exercises with Qualification & Validation work
- It is unclear whether SMEs in the area of Quality Risk Management itself are required in the Standard Guide" (O'Donnell, 2010)

Adamson highlights the commitment of senior management as being critical to the success of the QRM effort. He highlights some of the particular responsibilities as being implementation of a Risk Policy, implementation of Risk acceptability criteria and determining acceptable risk. He particularly highlights their responsibility for "accepting risks when the probability of occurrence of harm cannot be estimated" (Adamson, 2009). He goes on to specifically mention that assigning of ownership of risks is a specific step in the QRM process and also recommends a holistic lifecycle approach to QRM.

Similarly, Holmes (Holmes, 2008) also points to risk communication as a current implementation issue and in general highlights the inter-relationship of ICH Q8, Q9 and Q10 as being a critical factor.

It is significant that the regulators focus on Quality Risk Management rather than Quality Risk Assessment as their concern. They focus on a holistic approach to QRM and management responsibilities for implementing the programme. This illustrates the importance of recognising the place of QRM within the broader framework of a pharmaceutical quality system, effectively, implementing ICH Q9 as a part of ICHQ10.

2.8 The Impact of ASTM E-2500-07 on C&Q Practices

Wisniewski (2010) pointed out some of the issues surrounding traditional qualification, labelling it as a "broken process" (Wisniewski, 2010). He highlights "that IQ/OQ had become more intensive than PQ, that some organisations had refused to leverage commissioning, that automation systems were qualified separately and inefficiently and that deviations for trivial items were diluting quality unit attention". In the researchers experience, many organisations have already moved, in recent years, to a Lean C&Q model where leveraging of test information was commonplace.

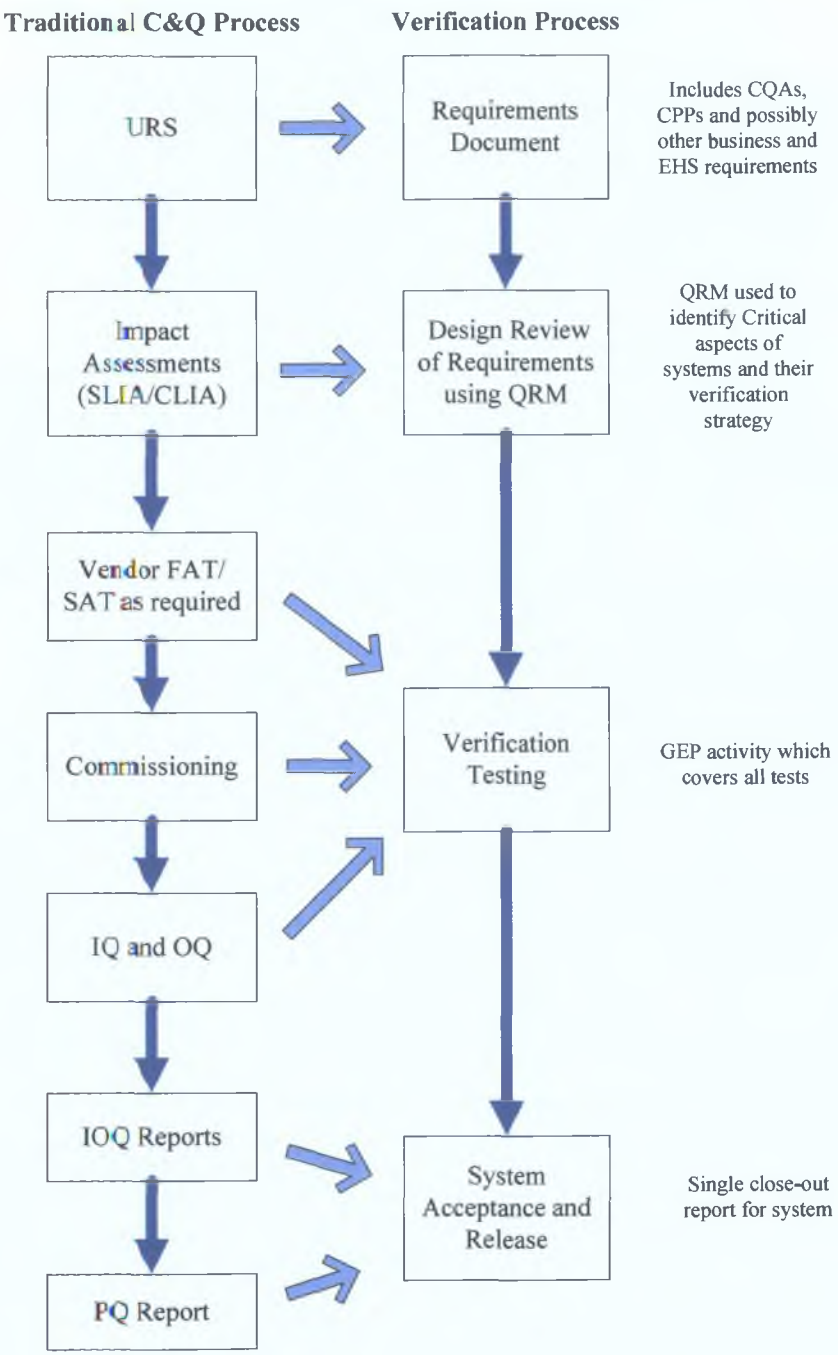
He highlights the main differences between traditional BG5 C&Q and the new ASTM E2500-07 verification model in terms of:

- Requirements document: Formally documented in the verification model, not normally documented in traditional C&Q.
- Protocols: In the verification model, risk assessments determine critical aspects for design, whereas in traditional C&Q, protocols are developed from templates.
- Testing: In the verification model, testing is a GEP exercise, whereas in traditional C&Q, the quality unit pre- and post-approves IQ and OQ documents. In the verification model, all documents with technical merit can be used as evidence of fitness for use, whereas in traditional C&Q, only quality approved documents can be used. In traditional C&Q the emphasis is on system performance, whereas in verification, the emphasis is on meeting process requirements.

Browne and Fischer (2010) highlight the differences between traditional C&Q, based on the Baseline Guide 5 V-model and the risk-based verification model. They highlight that testing is now a single activity based on the principles of GEP and that verification of automation is integrated with the verification of the manufacturing system. In the model proposed in this example, the URS of the traditional model is replaced by a requirements document, focussed on product/process requirements and a design basis document, focussed on other end-user requirements such as EHS. The impact assessment process is replaced by design review of the requirements document and the design basis document. Quality Risk Management is

applied at this step. Verification testing replaces both commissioning and IOQ. Verification testing is a GEP activity encompassing commissioning, FAT, SAT and IOQ. Finally, instead of separate PQ and IOQ reports, there is a single System Acceptance and Release report. A comparison of traditional C&Q versus the new verification model described by Browne and Fischer is shown in Figure 2.15.

Figure 2.15 Comparison of Traditional C&Q vs Verification



(Browne & Fischer, 2010, p.7)

ASTM E2500-07 highlights the role of Subject Matter Experts (SMEs) as a key concept in the verification approach: "Subject matter experts should take the lead role in the verification of manufacturing systems as appropriate within their area of expertise and responsibility" (ASTM, 2007). The guide goes on to say that "SME responsibilities include planning and defining verification strategies, defining acceptance criteria, selection of appropriate test methods, execution of verification tests, and reviewing results" (ASTM, 2007).

In the researchers experience the main stakeholders of a C&Q programme are the Quality Unit, the Engineering team (which includes the C&Q team) and the End-user team. Browne and Fischer (2010) outline at length the change to roles and responsibilities that moving to a verification model can bring. The revised role of the quality unit involves providing support, review and approval of:

- Requirements document.
- Project Verification Plan.
- Verification Quality Strategy – the process of identifying Critical Aspects and their corresponding test strategies, using QRM as required.
- Vendor assessment for leveraging of Critical Aspect testing
- Verification testing non-conformances related to a change in the Critical Aspect test strategy, acceptance criteria or design
- System Acceptance and Release report

Browne and Fischer (2010) also highlight that the revised role of the engineering group involves assuming responsibility for:

- Setting up the program, control that the program is applied correctly, coordinate verification activities and liaise with QA
- Interpretation of test results

Dolgin et al. (2010) point to the important new responsibilities of the End-user team. In the verification model, the user must now help to generate the requirements document, must participate in the manufacturing risk assessment, must perform the role of Subject Matter Expert of the manufacturing system and must accept the verified system. In the researchers experience that, in well-run projects in the traditional model, the end-user was already

actively involved throughout the C&Q process in an SME type role. In this role, the end-user could participate in construction walk-downs and could help with resolving deviations and expediting change controls (Dolgin, 2010).

An additional SME competence that may be required under the verification model is the role of a QRM SME. O'Donnell (2010) recommends that "given the importance of QRM in the entire E2500-07 approach; companies should consider developing and formally certifying individuals as QRM SMEs" (O'Donnell, 2010, p.21). Browne and Fischer (2010) make a similar point when they state that one of the lessons learnt from verification implementation is that "Risk Management principles need to be well understood and appropriately applied" (Browne & Fischer, 2010, p.26).

ASTM E2500-07 points to the use of vendor documentation as a key concept for implementation of the approach. Block (2010) highlights the changed role of vendors in the new verification approach. He states that vendors should be assessed and evidence obtained of the presence of:

- "An acceptable vendor quality system
- Vendor technical capability
- Vendor application of Good Engineering Practices such that information obtained from the vendor will be accurate and suitable to meet the purpose of verification" (Block, 2010).

Traditional C&Q does not normally allow the use of vendor documentation in the qualification effort. But with the emphasis switching to testing as a GEP exercise, this allows the use of vendor documentation, as long as the vendor is assessed and can demonstrate adherence to GEP.

ASTM E2500-07 recommends that change management is applied throughout the entire verification cycle. The risk and science-based approach makes it possible to apply engineering change management to the process in advance of acceptance, with the condition that any changes affecting critical aspects of systems should be communicated to the quality

unit (ASTM, 2007, p.5). After acceptance, the ASTM guide envisages operational change management. Change control procedures are laid down in existing SOPs in all biopharmaceutical companies and adoption of a verification model allows for these procedures to change.

2.9 The Benefits of the ASTM E-2500-07 Risk-Based Verification Approach

What are the benefits to be gained from implementation of a risk and science–based approach? Wisniewski (2009) makes the case for the risk-based approach and asserts that savings can be made as follows:

- "Elimination of non-value added practices
- Reduction of C&Q deviations
- Implementation of lean quality systems
- Simplification of new product introductions"

(Wisniewski, 2009)

Wrigley and Slock (2009) and Browne and Fischer (2010) estimated a saving on C&Q spend of in the range of 10 to 20 % by switching to a verification model. Wrigley and Slock (2009) stated that the savings had come from the:

- "Elimination of test duplication between commissioning & IOQ
- Achievement of more flexibility in execution of verification testing
- The ability to further leverage vendor testing"

(Wrigley & Slock, 2009)

Lucchesci points to other benefits that might be gained from adopting a risk-based approach to C&Q including:

- "More robust product/process
- Fewer complaints, returns, and warranty claims
- Fewer recalls and less subsequent FDA attention"

(Lucchesci, 2010).

Dolgin (2011) highlighted that risk-based C&Q was: "a little cheaper, a lot faster, focussed on patient risk, made possible resource reallocation and helped foster innovation" (Dolgin, 2011).

From a regulatory point of view, Thrussel (2010) stated that "EU regulators believed that effective and robust processes should be underpinned by the application of principles of Quality Risk Management and operated under an effective quality system" (Thrussel, 2010). This reinforces one of the benefits of QRM proposed by ICH Q9 that "effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight" (ICH, 2005, p.1).

2.10 Current Regulatory Approach – FDA Process Validation Guideline 2011

In January 2011, the FDA issued Process Validation: General Practice and Principles which updated the FDA's thinking on process validation based on industry experience gained since 1987 (FDA, 2011). It defines process validation as: "process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product" (FDA, 2011, p.4). It is important to note that the word "scientific" in this definition is in contrast with the word "documented" which was used in the 1987 guideline. Furthermore it defines qualification as referring to "activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly" (FDA, 2011, p.10).

This guidance aligns process validation activities with a product lifecycle concept and with ICH Q8, Q9 and Q10. It explains the product lifecycle concept as a concept which "links product and process development, qualification of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production" (FDA, 2011, p.2). It states that the basic principle of quality assurance is that a drug should

be produced that is fit for its intended use. It states that the principle incorporates the understanding that the following conditions exist:

1. "Quality, safety, and efficacy are designed or built into the product.
2. Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
3. Each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications".

(FDA, 2011).

For C&Q practices, these statements mean that process validation, which is a mandated activity, is now firmly aligned with ICH Q8, Q9, Q10 and the concept of a product lifecycle. It defines a product lifecycle as being a 3-stage process comprising:

- "Stage 1 – Process design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – Process qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3 – Continued process verification: Ongoing assurance is gained during routine production that the process remains in a state of control".

(FDA, 2011)

Stage 2 is further subdivided into two stages: (1) design of the facility and qualification of the equipment and utilities and (2) process performance qualification (PPQ). C&Q activities of facilities, equipment and utilities obviously occur during the first part of Stage 2. Importantly, the guidance defines qualification as "activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly" (FDA, 2011, p.11). It outlines the main activities of equipment qualification as:

- "Selecting utilities and equipment construction materials, operating principles, and performance characteristics based on whether they are appropriate for their specific uses.
- Verifying that utility systems and equipment are built and installed in compliance with the design specifications.

- Verifying that utility systems and equipment operate in accordance with the process requirements in all anticipated operating ranges".

(FDA, 2011, p.10).

The guideline here links together verification of the equipment performance with the process requirements (one assumes process requirements such as CQAs and CPPs) which makes the link with ICH Q8. The guidance states that the qualification process can be covered under a qualification plan which can "incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities" (FDA, 2011, p.11). This makes the link with ICH Q9 and introduces risk management into the qualification process. It states that the qualification plan should identify the tests, the acceptance criteria, the timing, roles and responsibilities, procedures for documenting and approving the qualification and the change control procedures. This aligns with the proposed verification plan identified in ASTM E2500-07 (ASTM, 2007, p.4).

Finally the guidance recommends a qualification report to document the qualification activities and that the quality unit should review and approve the qualification plan and report.
As demonstrated, the new process validation guideline, which is ultimately the source guidance document for all qualification activities, strongly aligns therefore with the science and risk-based approach of ICH Q8, Q9, Q10 and with ASTM E2500-07 which is referenced by the guidance.

2.11 Transition from C&Q to Verification – ISPE Good Practice Guide 2011

2.11.1 Overview of ISPE Good Practice Guide 2011

In October 2011, the ISPE published a Good Practice Guide entitled Applied Risk Management for Commissioning and Qualification with the stated purpose of facilitating the transition from traditional C&Q practices to science and risk-based approaches. This document builds on the science and risk based approach in documents already discussed in this dissertation and for the purposes of this review, only additional items will be discussed. The guide points out that some organisations may decide that the time and cost of converting from traditional C&Q to a purely science and risk-based approach may not be justifiable and so recommends a transitional approach which can build on an organisation's traditional practices and but also address the science and risk-based approaches.

2.11.2 C&Q Terminology

In the context of the Good Practice Guide, qualification is defined as "the demonstration of suitability for intended use which has been formally documented and approved" (ISPE, 2011, p.17). The guide describes "commissioning" as "a well-planned, documented and managed engineering approach to the start-up and turnover of facilities, systems and equipment to the end-user, that results in a safe and functional environment and that meets established design requirements and stakeholder expectations" (ISPE, 2011, p.17). The guide sees commissioning as being one of the primary activities that can generate the documented evidence of achievement of the qualified state. It sees design and specification as other primary processes and sees Factory Acceptance Testing and Site Acceptance Testing as part of commissioning. The guide sees that the traditional qualification terminology of Baseline Guide 5 and the verification terminology of ASTM E2500-07 as being equally suitable for use in demonstrating evidence of suitability for intended use.

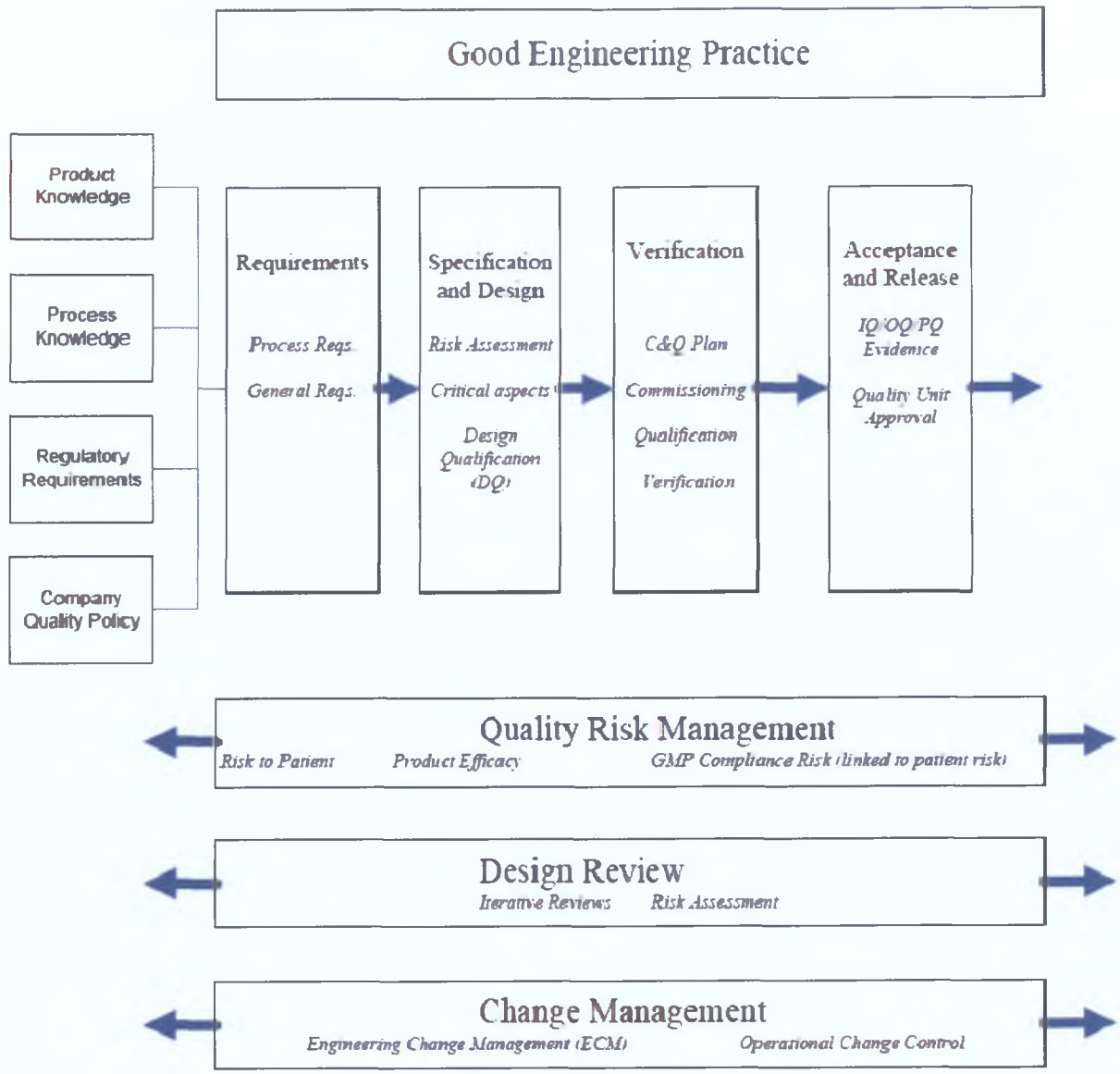
2.11.3 Transitional C&Q Process Flow

For those companies still pursuing transitional approaches, the ISPE Good Practice Guide proposes a modified ASTM E2500-07 process flow diagram. This is presented in Figure 2.16.

In this diagram the ISPE show that traditional C&Q terms such as DQ, IQ, OQ and PQ can be retained in the risk-based C&Q approach. Clearly, this is an advantage for a company with a very rigid qualification structure which is trying to adopt a risk-based approach but has limited time and resources available to it.

As with the ASTM E2500-07 approach, the Good Practice Guide emphasises the importance of a clearly defined set of Process User Requirements, which it states should include CQAs and CPPs. The guide also offers advice on how to deal with legacy products which may predate ICH Q8 and therefore may not have a set of developed CQAs and CPPs. It recommends "scientific review of the manufacturing instruction parameters combined with operational experience and batch quality history" as a basis for establishing PURs.

Figure 2.16 ASTM E2500-07 Process Flow Adapted to ISPE Good Practice Guide



(ISPE, 2011)

2.11.4 Changing Role of the Quality Unit

As the guide adopts the use of GEP throughout the C&Q process, the question arises as to the role of the Quality Unit. The guidance recommends that there should be six formal Quality Unit approval points in risk-based C&Q (ISPE, 2011, p.16):

1. Process User Requirements
2. Quality Risk Assessments
3. Critical Aspects and Acceptance Criteria
4. Commissioning and Qualification Plan
5. Qualification Summary Reports
6. Acceptance and Release of System

These approval points can all be seen in Figure 2.16 above. The guide also recommends that any change required to a document already approved by the Quality Unit should be approved by the Quality Unit.

2.11.5 Good Practice Guide Quality Risk Management Process

The guide proposes a much more detailed vision of how Quality Risk Management might proceed. It sees the key output of quality risk assessments as being the identification of Critical aspects. It proposes an iterative process linked to the design development of the system as outlined in Table 3. It continues to use the phrase DQ as it points out that this might be an existing regulatory agency expectation. The guide recommends that the participants in such a process should include relevant SMEs from all appropriate disciplines which could include:

- QRM team facilitator
- product development specialist
- process development specialist
- technology transfer personnel
- manufacturing operations end user
- engineering maintenance leads

- quality unit
- site quality control
- facility design lead
- process design lead
- equipment design leads, including vendors
- utility design lead
- HVAC design lead
- project management team leads

The guide highlights two factors that are essential to the success of the QRA effort are the necessity to have the required people and knowledge present at the assessment and also the level of experience of the team facilitator. The list of QRM participants highlighted here contrasts with the much smaller list of SLIA participants proposed in Baseline Guide 5 and listed in Section 2.2. The guide states that this approach may "generate significant project documentation" (ISPE, 2011, p.22). In this researcher's opinion, this process will be onerous for companies to follow. The iterative process described in Table 3 would involve allocating many of the key project personnel to risk assessment activities and could have implications for execution of their core duties, particularly at a busy stage of a project. This approach certainly poses a challenge to any biopharmaceutical company in terms of making such a quantity of resources available at such an early stage of a project.

Table 2.3: Steps and Project Stages for Risk Assessments

Step	Early Start	Finish By
Prepare Inputs (based on science and process knowledge)	Concept stage/ Project Scoping Document	Start of Preliminary Design
Process Focused Quality Risk Assessment	Start of Preliminary Design	End of Preliminary Design
Design Stage Quality Risk Assessment	End of Final Design	Construction Documents Approval
Risk Review (DQ)	After Completion of Design Stage Risk Assessment	Prior to IQ/OQ/PQ Preparation

(ISPE, 2011, p.22)

The guide aligns strongly with GAMP 5 and it quotes directly form GAMP 5 as follows:
"Where a computer system is regarded as one component of a wider manufacturing process or system, particularly in an integrated QbD environment, specific and separate computerised system validation may not be necessary" (ISPE, 2011, p.49). The Guide also uses the following quote from GAMP:
"For automated manufacturing equipment, separate computer systems validation should be avoided. Computer system specification and verification should be part of an integrated engineering approach to ensure compliance and fitness for intended use of the complete automated equipment" (ISPE, 2011, p.49).

In the section on SMEs, it highlights an Automation SME as a core team member, whose role is to "develop, verify and optimise automation and process control elements of manufacturing systems capability" (ISPE, 2011, p.60).
Traditional C&Q approaches tend to treat Control Systems Validation as a separate exercise. This is another example of how a risk based approach can impact on traditional C&Q practices.

2.11.6 Changes Required to Quality Management Systems

The Good Practice Guide also examines the challenges that organisations face when their Quality Management Systems predate ICH Q9 and risk-based GMP. It highlights numerous QMS challenges facing companies in a transitional mode of operation including:

- Changing the approval regime for IQ/OQ documents.
- Introducing an appropriate GEP programme
- Introducing an Engineering Change Management programme
- Allowing for leveraging of GEP-based commissioning work
- Increasing the flexibility of documentation procedures
- Allowing for vendor documentation to be used for C&Q purposes.

In particular, in the context of this research, the guide highlights that companies transitioning to a risk-based approach need to have a procedure for classifying systems and functions based on quality impact. It proposes establishing procedures, based on the guidance documents, on a pilot scale. It also proposes considering the use of all quality risk assessment tools and not just FMEAs and it also proposes streamlining the "qualified inventory" on an ongoing basis (ISPE, 2011).

2.11.7 The Role of a Risk Assessment Facilitator

The Good Practice Guide has a very clear vision of the role of a Risk Assessment Facilitator which it sees as an independent role, i.e. someone not already involved in the risk assessment as an SME. It states that the role of a facilitator is "to enable a team of technical SMEs to use their knowledge and judgement to conduct a risk assessment effectively" (ISPE, 2011, p.64). This is the most comprehensive description of this role in the literature. It is considered beneficial if the facilitator has experience in

- "SME-level knowledge of risk assessment tools and methods
- An understanding and appreciation of human heuristics
- An understanding of the culture of the organisation conducting the risk assessment regarding:
    - experience with risk assessment activities
    - level of cooperation or tension between functional groups
    - general risk tolerance of responsible management"

(ISPE, 2011, p.64)

Furthermore, the guide believes that a risk assessment facilitator should be able to "focus the risk assessment team" and "maintain a productive balance of discussion and decision-making" while also "act an early warning signal on the over-reliance on emotion versus analytical risks" (ISPE, 2011, p.64).

The guide describes some strategies for combating Human Heuristics, described earlier in section 2.7.2. Regarding the heuristic of availability, it is recommended that the facilitator should determine if someone on the team has had direct experience of the failure mode under

question as such a person's opinion may be considered more reliable than others. Regarding the heuristic of anchoring and adjustment recommends that, when assigning ratings during a brainstorming session, the facilitator should not allow any team member to verbalise an opinion until each team member has considered it themselves and formed their own opinion. The guide explains that, in keeping with Quality by design, there is a hierarchy of control strategies. It states that the best solution is to eliminate the risk by design where possible. If that is not possible, the guide contends that control of the risk through Automation is the next most preferable option and the least desirable risk control is to establish a procedural control, which by its nature is dependent on human actions, and therefore cannot be validated.

2.11.8 Recommendations for Organisations in Transition

The guide recommends that organisational policy, procedures and practice changes may be required in order to move to a risk-based approach. It proposes that these changes may include a shift from a system focus to a product and process orientation. For organisations using the SLIA process described in Section 2.2, it recommends changing the wording of the question so as to ask if the system directly impacts a CQA or a CPP, instead of asking if it comes into direct contact with the product. The guide recommends other changes which might be required of companies making the transition from traditional C&Q to risk-based C&Q including revisions to "quality systems and procedures" and "enhancements to the design review process".

2.12 Risk-Based C&Q Supporting Practices

ISPE Baseline Guide 12, entitled "Science and Risk-Based Approach for the Delivery of Facilities, Systems and Equipment" was published in June, 2011 (ISPE, 2011). Baseline Guide 12 updates Baseline Guide 5, according to the concepts of science-based risk management, Quality by Design and a focus on product and process understanding. It is strongly aligned with ICH Q8, Q9 and Q10 and ASTM E2500-07. In it, it provides detailed descriptions of the key risk-based C&Q supporting practices: Good Engineering Practice,

Risk Management, Design Review and Change Management. This dissertation has focussed on Risk Management, however, in order to implement fully a risk and science-based approach, an organisation must also implement the supporting processes. This section of the dissertation briefly explores these supporting practices and examines what their implementation might entail for an organisation transitioning to risk-based C&Q. Detailed study of these practices is considered outside of the scope of this dissertation.

2.12.1 Good Engineering Practice

Baseline Guide 12 defines Good Engineering Practice as follows:
"GEP uses established engineering methods, standards and practices that are used throughout the life cycle of the facility to deliver fit for intended use and cost effective solutions" (ISPE, 2011, p.63)

(ISPE, 2011).

The guide recommends embracing GEP as a philosophy, rather than "simply a collection of tools and templates" (ISPE, 2011, p.64). It proposes the principles of Deming's "Plan-Do-Check-Act (PDCA)" or the Six Sigma methodology of "DMAIC- Define, Measure, Analyse, Improve and Control" as useful methodologies in designing a robust GEP programme (ISPE, 2011, p.64).

The guide state that GEP activities include:

- "Selection of professional and competent personnel for project management, engineering design, procurement, construction, installation and commissioning
- Execution of design and installation that takes full account of GMP, safety, health, environmental, ergonomic, operational, maintenance, industry guidance and statutory requirements in conjunction with the necessary reviews to confirm these requirements have been met.
- Provision of appropriate documentation to provide evidence of compliance and support ongoing operation
- Provision of an appropriate degree of oversight and control that assures verification of design, construction, installation and commissioning activities demonstrate suitability for intended use.

- Provision of a well documented process of engineering change management to maintain traceability to approved requirements, respond in a timely manner to discrepancies, and ensure appropriate controls are utilised during project delivery.
- Additional practices required to integrate with an organisation's quality or engineering management system to support continual improvement once the verification process is complete".

(ISPE, 2011, p.65)

The guide identifies some of the key concepts for applying GEP to Project Engineering. Up-front planning, in order to identify required resources is recommended in order to avoid cost and schedule over-runs. The guidance also recommends a raft of project-specific procedures be applied to a project. While a library of these procedures may exist in an organisation, depending on the project, an assessment should be carried out in order to identify which particular procedures should be applied, if new procedures are required or if revisions are required to existing procedures. An extensive list of approximately 40 procedures is provided as guidance covering many activities in the life cycle including: project plans, quality assurance plans, quality risk management, verification planning and execution, change management, design review execution, URS preparation, P&ID walkdowns, receipt verification, vendor management, test execution, as an example (ISPE, 2011, pp.66,67). Furthermore the guide identifies further activities such as good documentation practice, project controls, project auditing, project planning, project logistics, project quality control, project turnover and project closure as activities that need to be controlled by a GEP programme.

In the researcher's opinion, the importance of the effort required upfront cannot be overstated. Any company planning on transitioning to risk-based C&Q should implement a formal GEP programme. For many organisations such programmes may already exist but may need to be updated to reflect the new approach. This is likely to require a significant effort in terms of time and resources. An organisation that does not have a formal GEP programme would face a considerable challenge and the need for significant investment. Such a company would have to identify resources to introduce a GEP programme. These

resources would then have to study company procedures and identify all of the additional or modified procedures and structures that would be required. Following this step, further resources may be required in order to write the new or updated procedures and carry out the training. In addition, an organisation may be facing a cultural change among its staff in relation to GEP which may be difficult to explain or may face resistance from existing stakeholders. It is clear, in this researcher's opinion that, risk-based C&Q cannot be implemented without this investment occurring upfront. As the baseline guide states:

"The implementation of GEP will prove critical to the successful application of the new science- and risk-based approach to facility start-up by providing simple, standardised and subject-matter led practices" (ISPE, 2011, p.63).

2.12.2 Design Review

The ISPE guide describes design reviews as "planned and systematic reviews of specifications, design, design development and continual improvement changes" (ISPE, 2011, p.73). It is recommended that design reviews should be performed throughout the life cycle of a manufacturing system in order to ensure that:

- "Product and process requirements are satisfied by the design.
- Critical aspects of the manufacturing system are appropriately addressed.
- Risks to product quality and patient safety have been identified.
- Unacceptable risks are mitigated by design or other means.
- Non specified aspects do not present unacceptable risks to product quality or patient safety".

(ISPE, 2011, p.73)

The guide also recommends that a multidisciplinary team, consisting of appropriate SMEs perform the design reviews and the life cycle of the design review process begins once a project is approved. It is recommended to adopt an iterative approach based on the design phases, which the guide defines as conceptual design, preliminary design and detailed design. In the science and risk-based model, the starting point for the design process is the

requirements document which has been generated by the user group and associated SMEs. The guide outlines that the requirements document explains "what" attributes of the product and process are critical to product quality and that the design should determine "how" to meet the requirements. The end user of the system is thus heavily involved throughout the design process. The guide also suggests that the supplier of the equipment may also be required to participate in the design reviews. The guide recommends that the design review process can take the form of a simple walkthrough of design material by the SMEs or a formal Design review by the project team or a peer review by external SMEs, not associated with the project.

It is recommended that consideration of the severity of potential deviations, the probability of occurrence of deviations and the probability of detection of deviations should be considered. The guide recommends that a risk assessment be carried out prior to design approval and unacceptable risks should be reduced to an acceptable level prior to approval. Finally, the guide states that the output from a design review process should be the achievement of "fit for intended use" consisting of realisation of a set of mitigated risks and residual risks that are acceptable through means of manual controls and SOPs.

The structured design review process proposed as part of science and risk-based C&Q is very different from traditional C&Q practices. It demands the participation of a cross-functional team of SMEs from the inception of a project. In turn, this requires careful resource planning and investment in order to achieve. It requires time to be built into the schedule to carry out the process and, in the author's opinion would lengthen the time required to carry out the design. Theoretically, risk–based C&Q should allow for shorter testing durations on site but this is somewhat offset by the longer design period involved in order to carry out the design review process. This further reinforces the point that any organisation intent on transitioning to risk-based C&Q needs to fully understand the changing work-flow and roles and responsibilities, in order to ensure that sufficient time and resources are allocated in order to successfully execute it.

Design review is complementary to the Quality Risk Management process as the main objective for the design review is to mitigate the risks to product quality in order to arrive at a declaration of "fit for intended use". In fact, in the risk-based C&Q example described in Section 2.8, Browne & Fischer described a process where formal design reviews were used to identify critical aspects, with further risk assessments used if required (Browne & Fischer, 2010). De Coninck and Dollard (2010), on the other hand, described a process where risk assessment was a defined, distinct step, occurring as a precursor to design review. Both approaches are aligned with the ISPE and ASTM guidance and demonstrate that the approach is flexible enough to allow different organisations to develop their own models, depending on their particular circumstances.

2.12.3 Change Management

Change Management is a regulatory requirement according to CFR211.100 and EU GMP Vol.4. ISPE Baseline Guide 12 defines a change as occurring when a system is "modified, altered, added to, removed or improved in a way that makes its functions or physical features different from what they were prior to the change" (ISPE, 2011, p.79).

Change management is a well-established practice throughout the biopharmaceuticals industry but the risk-based approach entails some key changes to the practice from traditional C&Q. In order to decide whether the change is beneficial or not and therefore acceptable, risk assessment is now required. For changes that occur before Acceptance and Release, the process is managed by the appropriate SME and changes affecting critical aspects must be communicated to the Quality Unit. For changes that occur after Acceptance and Release, operational change management is required. The guide states that "under operational change management, all changes related to specific requirements relative to product quality and patient safety require prior approval by the Quality Unit" (ISPE, 2011, p.80).

Implementing risk-based C&Q affords an organisation to simplify their change control procedure and place it under the control of an Engineering SME rather than the Quality Unit during C&Q. This change is a significant change to the responsibilities of the Quality Unit

and may well require a shift in organisational culture and thinking when implementing risk-based C&Q and is another example of the impact of the science and risk-based approach on C&Q practices.

2.13 Risk Based C&Q of Automated Systems – GAMP 5

In 2008, the ISPE issued GAMP 5 in response to the movement in the industry towards a science and risk-base approach. In terms of a science and risk-based approach, GAMP 5 is aligned with ICH Q8, Q9 and Q10 and also with ASTM E2500-07 and the ISPE's Product Quality Lifecycle Initiative (PQLI) (ISPE, 2010).

GAMP 5 identifies five key concepts that it applies in order to align with current industry thinking:

1. "Product and process understanding.
2. Lifecycle approach within a QMS.
3. Scaleable life cycle activities.
4. Science based quality risk management.
5. Leveraging supplier involvement."

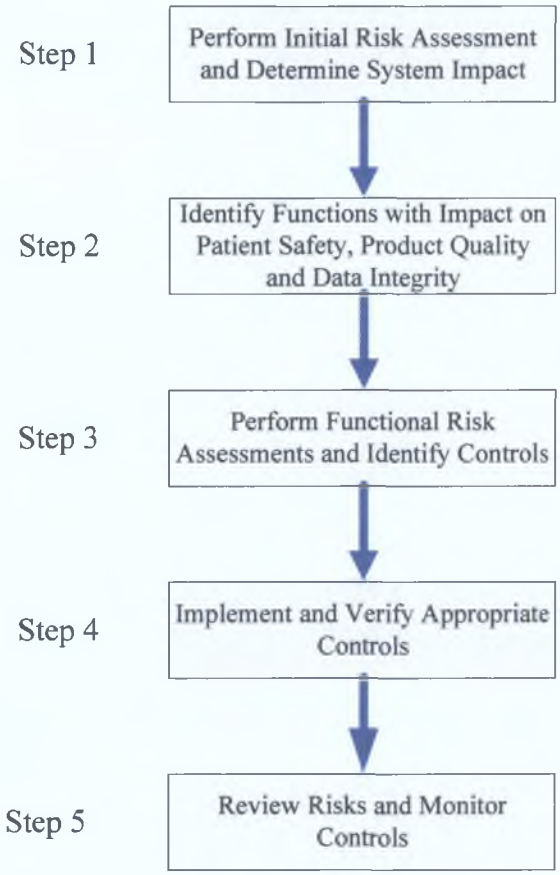
(ISPE, 2008, p.19)

Under the new approach, GAMP 5 states that "when a computer system is regarded as one component of a wider manufacturing system, particularly in a Quality by Design environment, then separate computer system validation may not be necessary" (ISPE, 2008, p.28). This is a change from the traditional C&Q approach where separate computer system validation activities were carried out. However it also states that this "requires both complete product and process understanding and that the critical process parameters can be accurately and reliably predicted and controlled over the design space" (ISPE, 2008, p.28).

GAMP 5 identifies a 5 step Quality Risk Management process which is described in Figure 2.17 below. In a review of GAMP 5 Martin (Martin & Perez, 2008) found that the GAMP 5 QRM strategy offered a pragmatic approach to "computer systems compliance" and was

consistent with ICH Q9. They found that that it was a "flexible and scaleable framework" and "assists with the identification and application of appropriate controls where they are needed" (Martin & Perez, 2008, p.7)

Figure 2.17: GAMP 5 Quality Risk Management Process



(ISPE, 2008, p.50)

2.14 Implementation of Risk-Based C&Q in the Biopharmaceuticals Industry

It is difficult to put an exact number on the number of biopharmaceutical companies who have implemented risk-based C&Q. References can be found from conference proceedings that many of the worlds blue-chip pharmaceutical and biopharmaceutical companies have begun implementation of risk-based C&Q (Block 2010, Browne and Fischer 2010, Brunelle 2011, Van der Steen 2009). In the researchers opinion, the evidence points to an industry in transition, an industry just beginning to implement the new approach. Some of the largest

companies have begun implementation relatively recently, but it seems there is no company claiming to have fully implemented a risk-based C&Q approach across all its sites.

3.0 RESEARCH METHODS

This chapter gives a description of the methodology that the researcher used in conducting this study into the development of Quality Risk management in the Biopharmaceuticals industry and its impact on C&Q practices.

3.1 Research Method – SME Interviews

The research objectives of this dissertation were laid out in section 1.3. The aim of this research relates to objectives 3, 4, 5 and 6. The research attempts to examine the status of QRM implementation in C&Q in the biopharmaceuticals industry, to evaluate the benefits of risk-based C&Q, identify any barriers to its successful execution and to explore the organisational and operational changes necessary in order to implement risk-based C&Q

Quality Risk Management implementation in the biopharmaceuticals industry is a very new topic and many companies are in a transition from traditional C&Q approach to new risk and science – based approach. The industry guidance on the subject, in the form of FDA, ISPE and ICH documents are very recent documents, published mainly within the last four or five years. As discussed in section 2.14, the picture that emerges is of an industry in transition, with many companies at varying stages of their initial implementation of the science and risk-based approach. The researcher felt, with such a new topic, that the findings of the literature review should be investigated further by collection of data.

Bearing this in mind, the research approach decided upon by the researcher was a qualitative one involving interviews with carefully selected industry figures. The intention was to learn from the experience and opinions of suitably qualified industry figures to gain an insight in to the current state of this topic in the industry. In the researchers opinion, surveys, as found in some conference proceedings (Dolgin, 2010), are not well suited to the research objectives of this dissertation. With many companies at varying stages of maturity in terms of implementation it is difficult to make comparisons between them and to arrive at quantified answers.

Five people were asked to participate in the interview process. Respondent A and Respondent B are both C&Q managers with a global engineering company, specialising in pharmaceutical and biopharmaceutical engineering projects. Both have approximately 15 years industry experience. Respondent C is a C&Q manager for a global biopharmaceutical company with recent experience of implementation of science and risk-based C&Q. Respondent D is a C&Q lead engineer with 15 years industry experience with experience in both traditional C&Q and risk and science based C&Q. Respondent E is a C&Q director of a global engineering company with 20 years industry experience and a deep knowledge of both traditional C&Q and risk and science –based C&Q. The researcher felt that this group of people provided an appropriate mix of different viewpoints to provide an accurate insight into current industry experience. The competencies represented range from engineering to quality and from engineer level through manager level to director level. All have hands-on experience of both traditional C&Q and risk and science-based C&Q.

3.2 Method of Data Collection

Focussed interviews were used, as described by Bell (2010). In a focussed interview a set list of questions are posed but the respondent is allowed to give their opinion in their own time. According to Bell (2010) interviews are more adaptable as the interviewer can "probe responses; investigate motives and feelings, something that a questionnaire cannot do" (Bell, 2010, p.161).

There are some potential drawbacks to interviews and that is the danger of bias. Bell quotes Sellitz on bias:

> "Interviewers are human beings and not machines, and their manner may have an effect on respondents"
>
> (Bell, 2010, p.169).

Awareness of the dangers of bias reminded the researcher to be continually vigilant and critical in interpreting the data.

3.3 Triangulation – Data Mining from Industry Conference Proceedings

Bell (2010) also recommends the importance of triangulation when collecting data. The researcher believes that by choosing to interview an engineer, a C&Q director and three C&Q managers, two of whom come from an engineering background that triangulation has been achieved. The researcher believes that the extensive study of the proceedings of ISPE conferences, as presented earlier in section 2.7 also constitutes a form of triangulation. A total of 47 different conference presentations relating to this topic were studied. In the main, these presentations were given by the very groups who are leading the implementation of risk-based C&Q in the industry. The researcher considers this an additional valuable second source of data.

The researcher believes that the study achieves validity. The implementation of risk and science-based C&Q in the biopharmaceuticals industry is being guided by the ISPE. The researcher believes that it is valid, therefore, to study the proceedings of the ISPE conferences on the matter and that this is an accurate source of information. The researcher also believes that conducting interviews with industry figures with the appropriate experience allows some of the issues to be explored in greater depth and allows a deeper insight into the matter than study of conference proceedings alone.

The researcher also believes the method is reliable. The dissertation sets out to gain an insight into the development of QRM in the biopharmaceuticals industry and the impact on C&Q practices. The author believes that the number of people with expertise, knowledge and hands-on experience in this topic is low and that therefore only a small number of respondents were suitable for interview. The author believes that securing the cooperation of these key individuals is the key to the reliability of the study.

4.0 RESULTS AND ANALYSIS

4.1 Introduction

This chapter reveals the results of the interviews with the industry experts. Eleven questions were asked and these questions were directly related to the themes raised in learning objectives 3, 4,5 and 6. The interview sheet is attached in appendix 1. In particular questions 2,3,4,5 and 6 in the interview were concerned with examining the current status of Quality Risk Management implementation in C&Q in the biopharmaceuticals industry (objective 3). Questions 7,8 and 11 examine critically the benefits of risk-based C&Q and attempt to identify barriers to its successful execution (objective 4). Question 10 explores the organisational and operational changes required by stakeholders in order to implement risk-based C&Q (objective 5) and question 9 asks if there are any recommendations that the respondents would make regarding the implementation of risk-based C&Q.

4.2 Familiarity with C&Q Practices of Different Companies

> Question 1: How many different biopharmaceutical companies' C&Q practices are you familiar with?

The purpose of the question was to determine the levels of experience and industry knowledge of the participants. All five respondents have experience of both the traditional C&Q approach and the science and risk-based approach. Respondents A, B and C all have experience of the C&Q approaches of a multiple of companies (approximately five each) and are all familiar with traditional C&Q, lean C&Q approaches involving increased use of leveraging of test information into qualification and also with implementation of risk and science based C&Q. Respondent D is a C&Q manager with a biopharmaceutical manufacturing company and also has in-depth knowledge both of the traditional C&Q approach and the risk-based approach (but manly with one organisation), while Respondent

E is a C&Q director with wide experience of the C&Q approaches, both traditional and risk-based, of all of the top-ten global pharmaceutical companies and numerous others.

4.3 Current Level of Industry Practice of Traditional C&Q

> Question 2: In general, what is your opinion of the percentage of companies that continue to practice C&Q according to the Baseline Guide 5 V-model approach?

The purpose of the question was to obtain an opinion from the experts on how widely traditional C&Q is still currently practised in the industry. Obviously, the only way to accurately obtain this figure is to simultaneously survey a representative number of organisations. This was not a feasible approach for the purposes of this research and the benefit of carrying out such a study is questionable at this juncture. Respondents A, B and D all shared a common perception that the number of companies still practising traditional C&Q was in the range of 90%. Respondent D pointed to the fact that the risk-based approach is relatively new and that the industry requires a period of time in order to phase out the V model. Respondent D also pointed out that "You simply cannot stop one model and implement the other. They are interdependent during transition phase".

Respondent E, however, who has the widest range of experience of the group, stated that all of the top-ten pharmaceutical companies (both biopharmaceutical and pharmaceutical) were in the process of moving away from traditional C&Q. Respondent E estimated that 20% of companies had moved to the risk-based approach, 40% of companies still practised traditional C&Q and the remaining 40% were in a transitional mode. Respondent E also observed that while many companies were not implementing the ASTM E2500-07 approach fully, many of these companies were implementing some of the eight core concepts of ASTM E2500-07, namely:

- Risk-based Approach
- Science-based Approach
- Critical Aspects of Manufacturing Systems

- Quality by Design
- Good Engineering Practice
- Subject Matter Expert
- Use of Vendor Documentation
- Continuous Process Improvement

The responses of Respondents A, B and D implies that the industry is really only beginning to implement the risk-based approach but the response of respondent E paints a slightly different picture. Respondent E suggests that the implementation of the risk-based approach has moved beyond its infancy and into a more transitional mode. The difference between the two opinions could be accounted for by the fact that respondent E possesses a greater awareness of industry trends, having experience across a wider range of companies. The question therefore is useful to allow an order of magnitude estimate of the level of current practice of traditional C&Q in the industry and thus, the level of implementation of risk-based C&Q in the biopharmaceuticals industry. For this project, the estimate would be that, currently, traditional C&Q is currently practised across approximately 90% of companies and that somewhere in the range of 10 to 20% of companies are implementing risk-based C&Q.

4.4 Current Level of Industry Practice of QRM in C&Q

> Question 3: In your opinion, what percentage of companies operates Quality Risk Management for their C&Q processes?

The purpose of this question was to try to achieve an order of magnitude estimate as to the level of implementation of Quality Risk Management (as defined by ICH Q9) in the biopharmaceuticals industry. Respondent B pointed out that, in line with the previous question, most companies still carry out impact assessments in relation to C&Q according to traditional C&Q practices and therefore the answer would be similar to the previous question which would be approximately 10%.

Respondent A and D both stated that all companies are implementing QRM for some of their processes such as Manufacturing Risk assessments, but pointed out that the number implementing QRM in C&Q was, in effect, the same 10% referred to in the previous question. Respondent E stated that while all the major companies were using quality risk assessment, "not many have rolled it into a complete quality risk management programme that gives a site holistic approach to QRM". Respondent E highlighted the use of the word "assessment" was deliberate as the respondent's opinion was that while companies were carrying out valid risk assessments, the risk communication aspect of their system was deficient.

In the researcher's opinion, the question successfully determined an order of magnitude estimate of the level of Quality Risk Management implementation in the industry. The question is directly related to the previous question as to the level of traditional C&Q practice in the industry. The conclusion of the researcher is that approximately 10% of companies are implementing QRM in their C&Q processes.

4.5 Alignment with ICH Q9

Question 4: Of the companies that operate Quality Risk Management, is it your opinion that their process is strongly aligned with ICH Q9, according to the following headings?

1. Risk Identification
2. Risk Analysis
3. Risk Assessment
4. Risk Reduction
5. Risk Acceptance
6. Risk Communication
7. Risk Review

The purpose of the question was to assess how well current QRM practices align with the industry guidance document ICH Q9. Respondent A believes that there are issues with Risk Acceptance, Risk Communication and Risk Review and raises the question of ownership of the risks and of the entire QRM process.

Respondent D believed that current QRM practices are well aligned with ICH Q9. However the respondent points out that there are many unanswered questions as to how the ICH Q9 implementation will be audited by regulators at site level. Respondent D states that "Organisations are still looking to find a sensible approach to Risk Management from Development phase to Manufacturing phase".

Respondent E stated that "companies put an enormous emphasis on the tools" but seem less inclined to approach QRM "holistically to support the product lifecycle". The respondent stated that QRM should be used in "a holistic way to support the process, rather than as a tool to support a phase in the product lifecycle". Respondent E also stated that it was their belief that Risk Communication was the biggest issue with ICH Q9 implementation currently. The respondent highlighted instances where regulators have been impressed with the conduct of the C&Q quality risk assessment but have found afterwards that the output of the risk assessments have not been communicated to operations staff appropriately and had not been implement in site procedures adequately.

It is clear that the respondents believe that, when implementing QRM, companies are focussing on the first five steps Risk Identification, Risk Analysis, Risk Assessment, Risk Reduction and Risk Acceptance but that this focus is too narrow and that there are deficiencies in industry practices regarding Risk Communication and Risk Review. There were no conflicting answers given to this question. In effect the respondents believe that the industry has focussed on effective quality risk assessment tools which are only part of ICH Q9. The respondents feel that a more holistic approach to the C&Q QRM process needs to be adopted by the industry. Adopting a more holistic, lifecycle approach would allow a greater focus on QRM activities which are outside of the risk assessment process itself, i.e. Risk Communication and Risk Review. Additionally

Respondent D has highlighted that there is also uncertainty in the industry regarding how the regulators will audit the practice.

4.6 Similarity of Industry QRM Practices

> Question 5: In your opinion, are different companies implementing broadly similar QRM processes for C&Q?

The purpose of this question is to assess whether there is evidence of different companies implementing broadly similar QRM processes. The researcher considered it useful to try to determine if a consistent and discernible pattern has emerged in the implementation of QRM in the biopharmaceuticals industry.

Respondents A and C were uncertain if a pattern could be discerned. Respondent B stated that the QRM processes are only the same if companies are implementing the same overall approach, that is, if different companies are implementing the ASTM approach, then the general QRM process is similar.

Respondent D, however, stated that QRM processes are not broadly similar and that there were differences between companies based on the type of manufacturing, i.e. API, drug product or biotechnology. The respondent stated that "the approach must fit the business needs and the return on investment".

The question highlights that the difference between the traditional C&Q model and the risk-based C&Q model. The traditional model proposed a relatively rigid structure and set of documents based on the V-model, as described in section 2.2. The document set required to execute traditional C&Q is broadly the same, in terms of DQ, IQ, OQ and PQ. Virtually every company adopted the same standard document set. Risk-based C&Q proposes an alternative model, one that is flexible and not necessarily the same from one organisation to another. The expectation is that risk-based C&Q is flexible and scalable and depends on the

situation at hand. As respondent D states, "it must match the business need". It must also be considered that, as very few companies have implemented the risk-based approach, it may be too difficult to discern a pattern at this point.

4.7 Process Flow of Industry QRM Practices

> Question 6: If companies are implementing similar QRM practices, can you briefly describe the overall process flow (of QRM processes for C&Q)?

The purpose of this question was to examine in greater detail the QRM processes that the respondents were familiar with and to demonstrate in some detail the actual QRM process as it has been implemented in the industry. Respondents B, C and D all described firstly the C&Q process in whish the QRM methodology was used.

Respondent B described the particular process flow as being:

1. Generation of Requirements document.
2. Carry out Risk Assessment to identify critical aspects.
3. Carry out a Final Design Review
4. Verification
5. Acceptance and Release.

Respondent C described the process as being broadly similar:

1. Generation of Requirements document
2. Design Review, including risk assessment, to identify critical aspects
3. Verification
4. Acceptance and Release

Respondent E took a different view of the overall QRM process flow. Respondent E has already stated that QRM needs to be approached from a holistic, product-lifecycle point of view rather than as an exercise to be carried out to support a single phase of that lifecycle. Respondent E proposed a more comprehensive QRM methodology. The respondent proposed that the first step of such a process is to outline all the processes, tests, systems, equipment and facilities related to the clinical and commercial manufacturing of products. Each of these processes should be linked to a risk assessment procedure. This risk assessment procedure can be any of the common risk assessment tools and a site method should be developed to select the most appropriate tool. A site procedure is then required in order to allow for collation of specific risks from all of these particular elements into one central list which is displayed on an overall monitoring tool which is maintained and reviewed at site management level. One such example of a risk monitoring tool is known as a Risk Dashboard and is especially useful at tracking progress on implementing mitigation measures. Respondent E also recommends that another site procedure would be generated to control how the risks are communicated across all concerned disciplines. From the C&Q team point of view, this would ensure that all risks can be communicated from the C&Q team to other departments and from other departments to the C&Q team. Together, the use of site procedures, enhanced communication system, site management risk review and use of risk dashboards can allow for improved compliance with the Risk Communication and Risk Review steps of ICH Q9.

The process flow is described in summarised in figure 4.1. The first step is to make a list of all of the elements which might include the following (C&Q is written beside elements impacting C&Q):

1. New product and process development and transfer. (C&Q impact)
2. Change control
3. Vendor selection and qualification (C&Q impact)
4. Supplier management (C&Q impact)
5. Corrective and Preventative actions (C&Q impact)
6. Complaints handling

7. Deviations (C&Q impact)
8. Inspections both internal and external
9. Training (C&Q impact)
10. New Regulatory requirement
11. Trends from quality indicators, periodic quality and product reviews.
12. New business strategies that may have a critical impact on the quality system.
13. Stability Monitoring
14. Validation approach (C&Q impact)

Individual risk assessments are carried out on each process independently by the relevant team and the high level risks are extracted from individual risk assessments and collated on to a site master list. Risks are communicated according to an SOP and are monitored at site management level using the risk dashboard tool which is shown in figure 4.1.

Figure 4.1: Proposed QRM Process Flow Including Enhanced Risk Communication and Risk Review

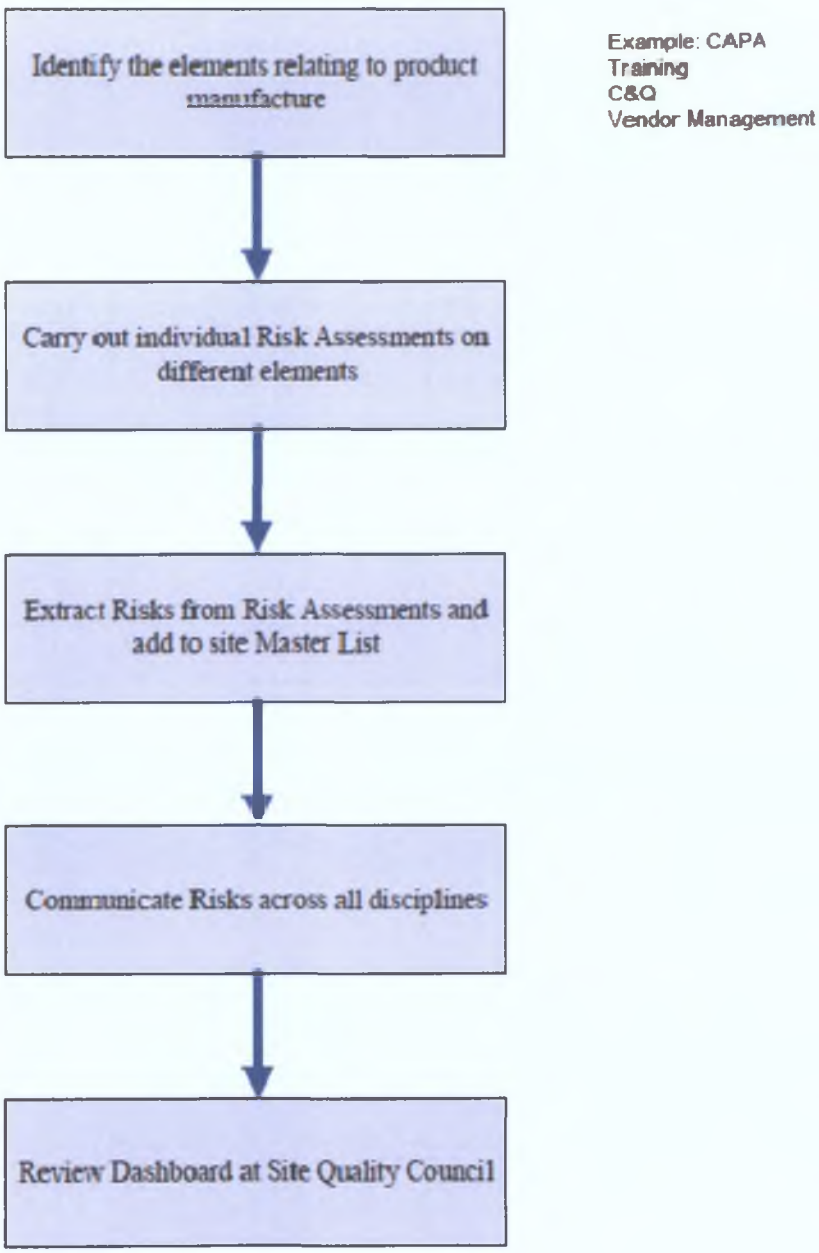
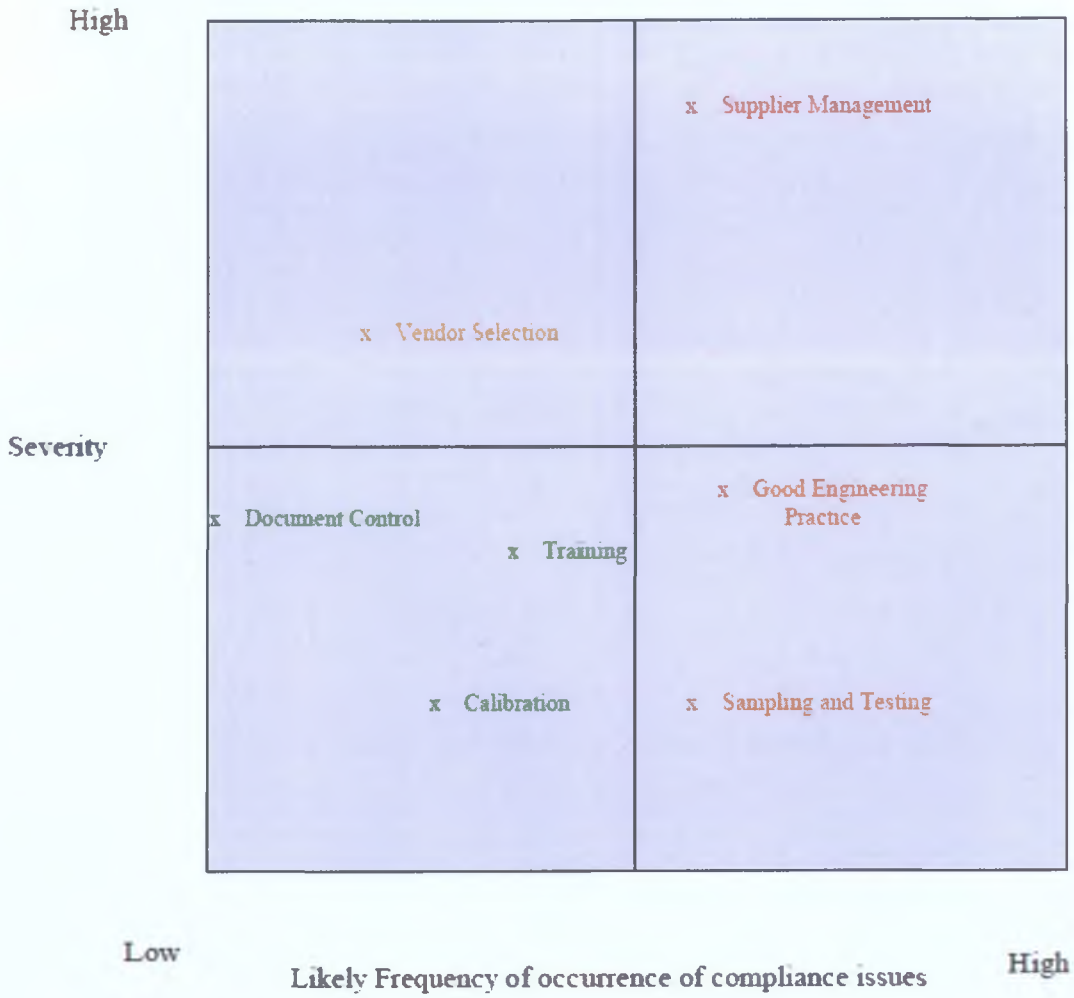


Figure 4.2 Risk Dashboard Tool for Quality Risk Management



In discussing the QRM processes of various organisations with the interview subjects a picture emerged firstly of the type of risk assessment process which has been implemented in organisations adopting the risk-based approach. In broad terms, the QRM process which is outlined by the respondents is similar to that outlined earlier in section 2.7.1.

It also became clear during the course of this discussion that the emphasis in industry up to now has leaned too heavily on the risk assessment tools and has not adequately dealt with the processes of risk communication and risk review. The Quality Dashboard, described in Figure 4.2, is a novel proposal and was put forward by Respondent E to deal with this deficit and is certainly a proposal that should be investigated in more detail by organisations.

4.8 Difficulties with Quality Risk Management Implementation in C&Q

> Question 7: Have companies reported difficulties with Quality Risk Management? If so, what is the nature of the problems reported?

The purpose of the question was to ascertain if any difficulties had been reported in industry examples of implementation of Quality Risk Management. Respondent A felt that a lack of Design Space information from process development scientists was the biggest obstacle to a successful quality risk management process. Respondent B also identified a lack of scientific information as an issue. Similarly Respondent C also highlighted poor identification of critical aspects as a concern and felt that it led to too many items being classed as critical and could lead to many items being classed as critical unnecessarily and an unnecessary use of resources.

Respondent D highlighted issues with implementing two of the supporting processes, Change Management and Good Engineering Practice, throughout the lifecycle of a project. Respondent D stated that "there is a significant bulk of work required on GEP foundations prior to leveraging to C&Q". Respondent D also highlighted the need to "document the Risk Management information in a template that all stake holders can use efficiently and effectively". The researcher feels that the risk management process proposed by Respondent E earlier could actually provide the tools to mitigate this concern.

Respondent E highlighted some concerns expressed by auditors that:

- Risk communication and review were not performed effectively
- The tool selected was not the most appropriate
- The team was not qualified enough to perform the risk assessment
- A more representative SME team was required in order to perform the risk assessment

The respondents highlighted many concerns that had already been highlighted in the conference proceedings and literature. Poor scientific data, poor tool selection, underqualified or insufficient SME resources, lack of effective risk communication and risk review are the main QRM difficulties highlighted.

4.9 Benefits of Implementation of Quality Risk Management in C&Q

> Question 8: In your opinion what are the main benefits to be realised from implementation of Quality Risk Management?

The purpose of the question was to examine and what benefits, if any, did the respondents feel had been realised by the implementation of Quality Risk Management in C&Q. The question could well have been more effective if it stated "In your opinion what are the main benefits to be realised from implementation of Risk-Based C&Q?"

Respondent A highlighted better drug product quality and, consequently, an expected reduction in number of process deviations and product returns as two expected benefits, while also believing that significant savings could be made on platform drugs. The respondent felt that platform drugs could offer a saving as the bulk of the science-based work could be done on the first drug and reduced expenditure would be required on the proceeding generations of drugs. Respondent A felt that there were not large savings to be made in the C&Q effort as the respondent cautioned that Lean C&Q practices had already accomplished much of this saving within the framework of traditional C&Q.

Respondent B stated that the main saving in their opinion was that, in theory less qualification work should be required, and so, duplication of effort could be reduced. Respondent B also felt that, although benefits were to be expected, the benefits had not yet been realised because the process is still in its infancy.

Respondent C felt that, in theory, one of the benefits that could arise was a reduction in the amount of resources required in order to execute a C&Q project. Respondent C felt however that it was too early to see any evidence of this in industry currently.

Respondent E felt that the entire process can prove very beneficial but only if Risk Assessments are carried out properly and the site Quality Management System is aligned well with ICH Q10. In this case, Respondent E believed that "operational efficiency, compliance efficiency and regulatory compliance" could be attained but only if the underlying prerequisites are set up correctly.

With successful QRM processes, Respondent E believed that "overall assessment of risk throughout the lifecycle is inherent" and doesn't require a separate, arduous effort. Respondent E felt that the benefits of greater efficiency and compliance could only be realised if risk management processes were built in to other supporting processes, such as change control, deviations management and customer complaints management, and if the risks from all of these processes are controlled at site level then the benefits can be realised.

Respondent E also felt that correctly-operated QRM processes offered a "more streamlined approach to CAPA, adverse events and offered more information to make decisions". Respondent E further clarified this to explain that in the event of a quality problem arising during processing, that access to information on critical aspects of the process would allow the production operations team to make better, more-informed decisions.

Respondent E also highlighted greater regulatory compliance. Respondent E felt that QRM cold allow an organisation to forge a "better relationship with the regulators" and make it easier for regulators to review the processes.

The answers to this question correlate very well with the benefits noted in conference proceedings in section 2.9. The respondents feel that implementation of risk-based C&Q holds out the prospect of many benefits for the biopharmaceuticals industry including:

- Increased drug product quality
- Reduced number of customer complaints
- Reduced number of process deviations
- Reduced duplication of effort during C&Q
- Greater operational efficiency and decision making
- Increased regulatory compliance
- More streamlined approach to CAPA

It is also notable that one of the respondents offered a qualification that in order to reap the benefits of the system, an organisation needed to implement the supporting processes as well as a Quality Management System based on ICH Q10. Indeed, Respondent D stated that benefits were only obvious 12 to 15 months after implementation.

4.10 Obstacles to Implementation of Risk Based C&Q

> Question 9: Have any benefits been realised by the implementation of Quality Risk Management in C&Q and are there any obstacles currently to the realisation of these benefits?

This question investigates the obstacles to the implementation of Quality Risk Management in C&Q. As the benefits of the risk-based approach have already been discussed, this question could more usefully have been phrased: "What are the obstacles to the implementation of risk-based C&Q in the biopharmaceuticals industry?"

The respondents highlighted a wide variety of obstacles to successful implementation of risk-based C&Q. Respondent A pointed out that many existing drugs may not have fully defined design space information and could form a major obstacle to implementation of the risk-

based approach. A key factor for the success of a product is the time to market and Respondent A also felt that, for new drugs, this could be adversely affected by the increased time spent defining the design space. In addition, Respondent A felt that senior management in some organisations could take the view that the cost and effort required in order to develop design space information could be questionable compared to the benefits to be accrued.

Respondent B focussed on the risk assessment process itself, stating that there is a huge amount of repetition and wasted effort in the risk assessments and that it is essential that the appropriate experts are invited to participate in order to streamline the process. Respondent B also highlighted the need for participants to have training and experience in Risk assessment tools and in the Quality Risk Management process, stating that, in the respondent's opinion that inexperienced participants are likely to be overcautious and overestimate the criticality of aspects, thus leading to a cumbersome and inefficient process. The respondent also stated that human behaviour while conducting risk assessments was an important factor which was currently inhibiting the success of Quality Risk Management and the resulting risk-based C&Q process. The researcher feels that tool selection could also be a contributing factor to some of these difficulties.

Respondent C largely agreed with the opinion of Respondent B and stated that the "first-time implementation was difficult" and that risk assessments took a long time to execute. On the other hand Respondent C felt that future implementation in the organisation should become smoother.

Respondent D stated that the "transition to QRM in C&Q is a journey that must be managed effectively and supported by Senior Management from top down. The transition must be a shared objective for all departments within the organisation in order to be effective". This continues a theme visited numerous times already in this research. One of the biggest obstacles facing risk-based C&Q is the reluctance of Senior Management in organisations to embrace the practice, take ownership of it and implement it in a meaningful way.

Respondent E focussed on the Quality Management Systems of biopharmaceutical manufacturers. Respondent E pointed out that many organisations, particularly larger ones, operate cumbersome quality management systems where procedures are written at global corporate level and not at site level. The respondent felt that this was an obstacle to introduction of a risk-based approach at site level as, in order to do it, global SOPs and standards may need to be changed. The respondent felt that such organisations could be discouraged from implementing the risk-based approach as it would prove difficult to implement the approach at one site in isolation. The respondent recommended that it is better if global corporate groups in organisations provided guidance only and local site SOPs were empowered to describe the process fully. This would allow greater flexibility to implement new approaches

Respondent E also felt that an obvious difficulty is the problem of changing people's mindsets and changing the ingrained cultures of certain organisations. The respondent also highlighted that risk-based C&Q brings a requirement for a front-loaded approach and consequently a front-loaded investment of resources in order to carry out risk assessments, vendor audits and other activities. Respondent E felt that there was a reluctance to make this upfront investment and that this would hinder the implementation of risk-based C&Q.

In summary, the respondents highlighted the following obstacles to implementation of risk-based C&Q:

- Lack of design space information for legacy drugs and the cost of generating the information involved compared to the benefits
- Problems with human behaviour, training and experience in carrying out risk assessments.
- Lack of senior management support for the process and lack of cross-departmental support
- Cumbersome and inflexible corporate-based Quality Management Systems making it difficult to implement new approaches at site level
- Difficulty in changing mindsets and organisational cultures
- Lack of commitment to the required front-loaded investment in resources.

4.11 Improvements to Implementation of QRM

> Question 10: Are there any improvements that you would suggest to the practical implementation of QRM in C&Q?

The purpose of the question is to examine any ways to improve the implementation of QRM in C&Q. Respondents A, B, C and D were all unsure and did not have any proposals. Respondent D stated that "at present the approach needs further audit by external regulators".

Respondent E focussed firstly on improvements to selection of tools. Respondent E stated that FMEAs are often too complex to examine the particular failure mode. The respondent stated that, very often, it is difficult to apply numbers to some of the occurrence probabilities and, in any case, a simpler tool like a Fault Tree Analysis or a Fishbone analysis is far more appropriate. This would serve to simplify the process, would make it easier for the participants to use and would produce more meaningful results.

Secondly, Respondent E proposed that manufacturing sites should write an overall site risk management plan and control the overall process with a site SOP. Respondent E also called for training in this proposed new procedure. In particular, training would be required in order to facilitate formal methods of communicating the risks to other functions in the organisation. A particular example, highlighted by the respondent is the need to find a method of communicating identified risks and critical aspects to production team leaders and supervisors. This would allow better decision-making by operational personnel during the production process itself.

4.12 Changing Role of C&Q Stakeholders

> Question 11: In your opinion how will the roles of the different C&Q stakeholders change with the implementation of Risk-based C&Q? In particular, can you consider the role of the End User Team, the Quality Unit, the C&Q team and the Engineering team?

The purpose of the question was to evaluate how the roles of the major C&Q stakeholders would change in the transition from traditional C&Q to risk-based C&Q.
Respondents A stated that the "Quality unit need to accept and own the risk if they're happy that the Quality by Design work is done". Respondent A stated that Quality Unit sign-off would be less but the Quality Unit needs to buy in to the change. Respondent A also pointed to the changes that Clinical teams, Technical Operations teams and technology transfer teams must make in order to be in apposition to support the process. Respondent A, was in no doubt, however, that the biggest impact was on the Quality Unit.

Respondent B also focussed on the Quality Unit and stated that, in the respondent's opinion, the Quality unit would become "less hands-on" and would hold more of an overseer role, agreeing procedures and reviewing reports rather than individual test documents.

Respondent D's response regarding the Quality Unit was in line with the responses of Respondents A and B. The respondent stated that there was a "better focus for the Quality unit as their effort is only concentrated on CPP / CQA information". This was developed further by the respondent who highlighted the increased role of the Engineering team in place of the Quality unit and the use of Good Engineering Practice in the verification effort. The respondent stated that there was a "much better use of Engineering and Automation resources" and also that there was less test documentation than in traditional C&Q.
Finally Respondent D stated that the end user would now also be involved in process understanding at the outset".

Respondent E stated that the role changes were as described in the ISPE Good Practice Guide (ISPE, 2011, p 60), and discussed earlier in this dissertation in Section 2.10. In particular, Respondent E also highlighted the earlier role of manufacturing and technical operations teams in defining the verification process.

4.13 Cost or Time Savings from Risk-Based C&Q

> Question 12: In your opinion, will risk-based C&Q lead to savings in terms of finance and schedule compared to BG5 V-model C&Q? If so, where will the savings be gained?

The purpose of the question was to assess if any financial savings could be made from adopting Risk-based C&Q. This question elicited a cautious response from all respondents. Respondent A took the view that savings were potentially possible but the introduction of leaner C&Q practices in recent years had seen many savings and the elimination of some of the more wasteful C&Q practices. Respondent A pointed out that the profile of the capital spend would be changed in risk-based C&Q. In respondent A's opinion the C&Q cycle time would be shortened but resources would be allocated differently. Respondent A also thought that Risk-based C&Q would lead to front-loading of resources and that C&Q personnel would be involved earlier. Respondent A also felt that the changing role of the Quality Unit would mean less Quality Unit resources would be required. However, Respondent A felt that, as more was now expected of the vendors and contractors, costs in these areas would rise.

Respondent B's assessment was that the resource allocation required in order to execute risk-based C&Q was unknown at this early stage and that the financial savings were unknown at this time.

Respondent D concurred with this analysis, stating that one needed to be "careful when communicating a saving based on the transition to ASTM E2500 Risk Based approach.

Respondent D pointed to the "investment required at the outset in reviewing the full Project Lifecycle and developing the strategy". Respondent D stated that that a saving can only be achieved by doing less or using fewer resources but the risk-based approach has not resulted in less work but instead in different tasks and different roles and responsibilities with a specific focus on supporting product quality and patient safety. Respondent D summarises by stating that "in summary the transition was not driven by costs, it was driven on business needs and a common organisational objective to implementation of ICH Q8 / 9 /10".

Respondent E stated that the extent on savings depended very much on the starting point of the individual company. The respondent believes that, if a company had adopted leaner C&Q practices in the traditional model then it is unlikely that that company would see a big difference in C&Q costs in switching to the risk-based approach.

Respondent E also makes the point that while C&Q costs might reduce, overall project costs might not as vendor costs might increase, due to the increased verification work expected from vendors. Respondent E also believes that additional costs can be incurred in the initial transition from the traditional C&Q approach to the risk-based approach. The respondent believes that, in order to minimise costs at the initial implementation stages, it is important to define the approach in its entirety from the beginning and put in place the structures and resources.

5.0 CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction

The overall aim of this research was to advance an understanding of the implementation of both Quality Risk Management and risk-based commissioning and qualification practices. The research objectives for this dissertation are outlined below:

1. Trace the development of both commissioning and qualification and risk management practices over the last 25 years.
2. Describe the Quality Risk Management process as it applies to commissioning and qualification of facilities, equipment and utilities projects in the biopharmaceuticals industry.
3. Examine the current status of Quality Risk Management implementation in C&Q in the biopharmaceuticals industry.
4. Examine critically the outcome of the early examples of implementation of risk-based C&Q to evaluate the benefits and identify barriers to successful execution
5. Explore the organisational and operational changes required by stakeholders in order to implement risk-based C&Q.
6. Formulate recommendations regarding the implementation of risk-based C&Q.

This section will revisit the research objectives above, summarise the findings of this research work and offer conclusions based on the findings.

5.2 Research Objectives: Summary of Findings and Conclusions

5.2.1 Research Objective 1 – The Development of C&Q and Risk Management

The FDA Process Validation document of 1987 is a seminal document in the development of C&Q methodology in the biopharmaceuticals industry. It introduced the concept of process validation and identified a system-based approach to equipment validation including execution of installation and process performance qualification activities. While the

document did link the qualification activities to process conditions it did not introduce the concept of risk management.

In 2001, following many years of increasing costs associated with commissioning and qualification, the ISPE introduced Baseline Guide 5 which provided for the first risk-based approach to commissioning and qualification. The risk assessment procedures in this guidance, called impact assessments, were equipment-based, a so-called bottom-up approach, which did not focus on the product quality attributes or the critical process steps. The C&Q process arising out of Baseline Guide 5, called the V-model, was a rigid prescriptive process, depending on a set structure of documents with heavy involvement of the Quality Unit for pre and post approving of documents and changes. It has become the industry standard approach to C&Q and is known as traditional C&Q at this stage.

The publication in 2004 of the FDA initiative, "Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century", changed the focus of C&Q from being an equipment system based activity to focusing on a science and risk-based approach. The three pillars of the new approach would be a risk-based approach, a science-based approach and a Quality Systems approach.

In conclusion, the traditional system-based C&Q approach which has developed in the industry since 1987 is being completely refocused on the new priorities of scientific knowledge and risk management.

5.2.2 Research Objective 2 – Description of the QRM Process in C&Q

Following the publication of the FDA CGMP for the 21st century initiative, three pivotal documents were published by the International Council for Harmonisation; ICH Q8, ICH Q9 and ICH Q10. ICH Q8 outlined a standard framework for the industry to express its scientific knowledge of its products and processes by defining the basic concepts of Critical Quality Attributes and Critical Process Parameters which allow for the design space of a product to be developed. The design space would be considered the combination of variables and parameters required to provide quality assurance.

ICH Q9 defined the framework for the Quality Risk Management approach that the regulators expected the industry to adopt. It laid out a holistic; product lifecycle approach to

quality risk management, taking the scientific knowledge generated using ICH Q8 and explaining how modern risk management processes could be used in order to ensure the high quality of the drug to the patient. It advocates a much more thorough, far-reaching and product quality-focussed approach than the impact assessment process of traditional C&Q. Importantly it highlighted the need for Risk Review and Risk Communication as part of a Risk Management approach rather than simply a Risk Assessment approach.

ICH Q10 provided industry with a framework for an overarching Quality Management System. It is only within an effective Quality Management System that an organisation can realise the full benefits of the science and risk-based approach.

Arising out of the FDA and ICH science- and risk-based initiative, came the ASTM E2500-07 document which proposed an entirely new model for C&Q, which it entitled verification. ASTM E2500-07 introduced the additional key concepts of Critical Aspects of Manufacturing Systems, Subject Matter Experts, Good Engineering Practice, Use of Vendor Documentation and Continuous Process Improvement. It proposed a four step process of (1) Requirements, (2) Specification and Design, (3) Verification and (4) Acceptance and Release and proposed that supporting practices such as Quality Risk Management, Design Review, Good Engineering Practice and Change Management should be applied throughout.

The practice of Quality Risk Management within C&Q is thus defined. QRM is a step-wise methodical process as per ICH Q9, taking scientific knowledge as its start point and placed within the framework of a Quality Management System which can allow for effective Risk Communication and Review. Within the C&Q effort, it is applied throughout the four stages of the C&Q lifecycle and is interlinked with the other three supporting processes.

5.2.3 Research Objective 3 - Current Status of QRM Implementation in C&Q

In terms of implementation in the industry, the interviewees estimated that approximately 10-20% of companies were implementing risk-based C&Q.

Numerous tools such as preliminary hazard assessments FMEAs, Boston matrices and fishbone analyses are reported in the literature. Tool selection has been highlighted as a key factor in the success or failure of the risk-based approach. No one tool can be considered as a standard for Quality Risk Management and it is preferable instead to standardise on a tool selection policy instead. The interviewees also highlighted that a range of risk assessment tools can be used. The approach can be flexible and scaleable from one project to another and from one organisation to another.

The interviews and the literature highlighted that a feature of the current implementation of QRM is that organisations are focussing too heavily on risk assessment tools and not enough on the process as a risk management system. The regulators have focussed on this deficiency and have advocated a holistic approach with more senior management involvement and ownership of the process and better acceptance of residual risks and better communication of the output of risk assessments. One of the interviewees advocated using a Quality Dashboard risk monitoring tool as part of a company-wide Risk Review and Risk Communication system. The proper functioning of this system would hinge on the implementation of a company-wide Quality Management System as defined in ICH Q10.

To conclude, the industry has been focussing too heavily on the risk assessment tools, at the exclusion on the Quality Management Systems that underpin the entire effort. Quality Management Systems need to be upgraded to be fit-for-purpose to support science- and risk-based approach to C&Q.

5.2.4 Research Objective 4 – Benefits of and Difficulties with Risk- Based C&Q

ICH Q9 asserts that the implementation of Quality Risk Management can provide an organisation with further assurance of high quality drug product, improved decision making and greater assurance of regulatory compliance.

The benefits of risk-based C&Q reported in the literature included elimination of wasteful practices, reduction in deviations, elimination of test duplication, more robust process and product, fewer complaints and returns, less regulatory attention and greater flexibility in testing. In the literature there is even a reported financial saving of in the order of 10 to 20%. The benefits reported in interviews largely correlated with these benefits, however all of the interviewees explicitly ruled out claiming a financial saving. There were a number of reasons for this, including: (a) some companies were already operating a lean C&Q model, (b) the change to a verification model meant the workload was distributed differently but not necessarily reduced and (c) as the implementation is only at the initial stages, a lot of upfront investment is required.

In conclusion, the benefits of risk-based C&Q envisaged by ICH Q9 have been realised by the organisations that have implemented this approach. However, significant financial savings have not been realised at this juncture.

There were many difficulties reported in the literature with the new approach. Some of the difficulties cited were that Good Engineering Practice was not established well enough, there was not enough training on risk assessment tools, poor participation of stakeholders and participants were susceptible to human heuristic behaviour, brainstorming sessions were poorly structured, risk communication was poor and there was difficulty getting buy-in from the Quality Unit.

The interview respondents cited a very similar list of difficulties but also had experience of additional difficulties including: lack of design space information and therefore difficulty identifying critical aspects, poor tool selection, lack of risk assessment tool training, poor selection of risk assessment team difficulties with new approach to GEP and change

management and lack of an effective Quality Management system. The industry experts and the literature are largely in agreement with the nature of the difficulties seen in the implementation of Risk-based C&Q.

As implementation of Risk-based C&Q is only beginning in the industry, many problems are to be expected. Currently these problems mainly stem from lack of a Quality Management System, poor application of both scientific knowledge and risk management tools and methods and also from lack of development of supporting practices such as Good Engineering Practice and Change Management.

5.2.5 Research Objective 5 – Organisational Changes with Risk-Based C&Q

The ISPE Baseline Guide 12 and Good Practice Guide offer detailed guidance on the changing operational methodology and organisational roles and responsibilities necessary in order to implement science and risk-based C&Q. The role of the Quality Unit would fundamentally change from one of heavy involvement in day-to-day testing in terms of pre-approval, post-approval and review of documents to one of overseer, involved in approval at a number of pre-defined junctures in the project. The focus of the Quality unit would switch fundamentally to user requirements and critical aspects of manufacturing systems, to involvement in their identification, approval of their verification strategy and acceptance of the verification and release of the system to manufacturing.

Verification testing itself would become the responsibility of an Engineering Subject Matter Expert and standards of GEP would apply to the testing. The testing would not be duplicated and vendor documentation would be heavily relied upon. Test documents pre- and post-approved by the Quality Unit would no longer be required. This would place a heavy burden on a site's Good Engineering Practice programme and it is likely that many sites would have to either institute an entirely new GEP programme or significantly upgrade an existing programme.

Design reviews and risk assessments would become a structured, iterative part of the design process and would require involvement from a wide range of stakeholders, particularly the end-user, at a much earlier stage than in traditional C&Q. The effort to develop GEP programmes and support the design review and risk assessment process will require significant up-front investment from the management of an organisation.

Automation systems would be considered part of the primary equipment system for commissioning and qualification purposes and the change control procedure would become an engineering change management procedure rather than a Quality Unit-led procedure as it is currently.

The literature recommends the creation of a role of Quality Risk Management Facilitator who is outside of the project but is proficient with risk management tools. All of the stakeholders and SMEs will require training in risk management techniques.

The responses of the interviewees agreed with these findings. The interviewees also highlighted the changed role of the Quality Unit and the increased reliance on GEP in testing.

The implementation of risk-based C&Q changes the duties and the roles and responsibilities of all the main stakeholders in a project, the Quality Unit, the Engineering team and the End User team. The changes outlined require investment in an upgraded quality management system, scientific knowledge management system, GEP programme, risk management programme, vendor management programme as well as an investment in the resources to ensure these issues are tackled at the outset of a project and to plan so as to ensure sufficient resources are available throughout a project to support it's entire lifecycle.

5.2.6 Research Objective 6 – Recommendations Regarding Implementation of Risk-based C&Q

Quality Risk Management has been considered by industry mainly in terms of risk assessment tools up to now. Site senior management needs to take greater ownership of this issue. The industry needs to adopt Quality Management Systems that allow for effective risk review and risk communication. Site-wide Quality Risk Management plans and procedures need to be generated in order to control this process. Use of tools such as the quality Dashboard should be considered. Consideration should be given to electronically linking the Quality Dashboard tool itself to the output of all the risk assessment processes on site so that all high risk items are updated automatically.

An organisation needs to also put in place the scientific knowledge management systems, as per ICH Q8, to identify critical quality attributes and critical process parameters. For legacy drugs, methods need to be designed to use prior production experience to identify a design space for these drugs.

Sites need to consider the appropriateness of the risk assessment tools themselves. Very often, companies choose FMEA based tools and ignore simpler, more appropriate tools such as fishbone diagrams or hazard analysis tools. Companies need to adopt a tool selection policy that is sufficiently flexible. All participants to a quality risk assessment process require training and companies should consider training some staff to be specialist risk assessment facilitators. The facilitators should be able to reduce the effects of human heuristics.

Once the basic requirements of ICH Q8, Q9 and Q10 are implemented an organisation can look at the requirements for risk-based C&Q. An organisation transitioning to the risk based approach must reassess its Good Engineering Practice programme and upgrade in the event of any gaps being identified. For some organisations this might require an entirely new GEP programme. Organisations must be prepared to make an upfront investment to make

resources available to support the risk assessment and design review process and to work with the vendors to improve the standard of their documentation to the required level.

Organisations should prepare for the changing role of the Quality Unit well in advance, including changing the change control system to an Engineering Change Management system.

5.3 Recommendations for Further Study

The Dissertation highlighted three particular areas where the author feels further study would be beneficial:

1. The practical implementation of ICH Q8 requires further study. It was noted that in some cases there was a lack of detail of product Critical Quality Attributes, Critical Process Parameters and the Design Space information and this proved an obstacle during quality risk assessments.
2. The upgrade of Quality Management Systems to reflect the new risk and science-based approach. It was repeatedly highlighted that a more holistic approach to Quality Risk Management was required, one where QRM was enshrined in a post-ICH Q10 Quality Management System
3. The implementation of a formal Good Engineering Practice programme, focussing especially on companies where no such programme exists. GEP underpins the entire risk-based C&Q approach and very many companies may not have formal programmes.

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APPENDICES

Appendix 1: Interview Question Sheet

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M. Sc. Biopharmaceutical Science 2012

Interview Questions

Thesis Title: Implementation of a Quality Risk Management Approach to Commissioning and Qualification in the Biopharmaceutical Industry

Question 1: How many different biopharmaceutical companies' C&Q practices are you familiar with?

Question 2: In general, what is your opinion of the percentage of companies that continue to practice C&Q according to the Baseline Guide 5 V-model approach?

Question 3: In your opinion, what percentage of companies operates Quality Risk Management for their C&Q processes?

Question 4: Of the companies that operate Quality Risk Management, is it your opinion that their process is strongly aligned with ICH Q9, according to the following headings?

1. Risk Identification
2. Risk Analysis
3. Risk Assessment
4. Risk Reduction
5. Risk Acceptance
6. Risk Communication
7. Risk Review

Question 5: In your opinion, are different companies implementing broadly similar QRM processes for C&Q?

Question 6: If companies are implementing similar QRM practices, can you briefly describe the overall process flow (of QRM processes for C&Q)?

Question 7: Have companies reported difficulties with Quality Risk Management? If so, what is the nature of the problems reported?

Question 8: In your opinion what are the main benefits to be realised from implementation of Quality Risk Management?

Question 9: Have any benefits been realised by the implementation of Quality Risk Management in C&Q and are there any obstacles currently to the realisation of these benefits?

Question 10: Are there any improvements that you would suggest to the practical implementation of QRM in C&Q?

Question 11: In your opinion how will the roles of the different C&Q stakeholders change with the implementation of Risk-based C&Q? In particular, can you consider the role of the End User Team, the Quality Unit, the C&Q team and the Engineering team?

Question 12: In your opinion, will risk-based C&Q lead to savings in terms of finance and schedule compared to BG5 V-model C&Q? If so, where will the savings be gained?