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The development of a Quality Risk Management solution designed to facilitate compliance with the risk-based qualification, validation and change control GMP requirement of the EU

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The development of a Quality Risk Management Solution designed to facilitate compliance with the risk-based Qualification, Validation & Change Control GMP requirements of the EU

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Volume 1 of 2

Abstract

This research work was concerned with investigating the risk-based regulatory requirements that are currently in place in the European Union governing the manufacture of medicinal products. The main goal of this research was to develop a practical Quality Risk Management methodology that served as a solution for facilitating compliance with the EU GMP requirements in the area of risk-based Qualification, Validation and Change Control, and which was fully in line with the principles and guidance of ICH Q9, on Quality Risk Management.

Following extensive testing and evaluation activities with a range of key stakeholders, including the pharmaceutical manufacturing sector in Ireland, the UK and the US, and GMP Inspectors from a wide range of countries, this work resulted in a formal, readily usable, rigorous and complete Quality Risk Management methodology. It is designed to facilitate compliance with the risk-based qualification, validation and change control GMP requirements of the EU, and is fully in line with ICH Quality Risk Management principles and guidelines. A practical and detailed training programme on the use of this methodology is also presented. This provides comprehensive training materials for facilitating training activities, as well as a documented strategy for the provision of such training in a timely and resource-efficient manner.

In a comprehensive benchmarking exercise, this approach to Quality Risk Management was compared with the application of Risk Management in two industries that are considered mature and advanced in their application of Risk Management principles and methodologies. These were the US aeronautics industry, as represented by the work of the National Aeronautics Space Administration (NASA), and the US nuclear power generation industry, as represented by the work of the US Nuclear Regulatory Commission (NRC). The methodology performed very favourably in this benchmarking exercise, and many examples of common best practices were identified.

The Quality Risk Management methodology developed in this work has attracted wide interest, not only from within the pharmaceutical manufacturing industry, but also from the GMP Inspectorates of several countries, from academic bodies involved in the teaching of pharmacy and pharmaceutical-related sciences in Ireland, from the

publishers of research journals involved in pharmaceutical science, among others. The methodology has already found application in several multinational pharmaceutical manufacturing and other companies, and has served as a valuable educational and training resource in the practical application of Quality Risk Management in the GMP environment.

The application of formal Quality Risk Management methodologies in the EU pharmaceutical manufacturing environment is still at its early stages, relative to that in other industries, and several opportunities to further develop and build upon this research work have been identified. The intention behind these recommendations for further work is to promote the continued development of Quality Risk Management methodologies and approaches within the GMP environment, so that the risks posed by medicines to patients and animals may continually be reduced and managed.

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Aoibhinn beatha an scolaire bhíos ag déanamh léinn.

Declaration

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

This thesis was prepared according to the regulations for postgraduate study by research of the Dublin Institute of Technology and has not been submitted in whole or in part for an award in any other Institute or University.

The work reported on in this thesis conforms to the principles and requirements of the Institute's guidelines for ethics in research.

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

Candidate Signature: Laura O'Donnell

Date: 11/2/2008

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On a personal level, doing this PhD work would not have been possible without the support and patience of many friends, my brothers and sisters, and my extended family. Thank you all.

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I would like to thank Mitsuko's parents, Mr. & Mrs. Oseto in Tokyo, for providing great hospitality and a very comfortable home for me to begin writing the final chapter of this thesis when on holiday there in late 2007. I am sure they wondered what kind of crazy guy their daughter had married, who spent all hours banging away on the laptop while visiting them. Thanks also to Takuo and Yoko Takeuchi in Kamakura, Japan. I hope we will have many more trips together, as the years come and go.

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As I write this, I think of Sonny Thomas McKee, my nephew, age almost 3 months. His Great Grandmother is Nellie Byrne, my Granny, aged almost 100 years! Together they make up a century of hope, wisdom and life. I dedicate this thesis to them.

Finally, to Mitsuko, my better half. Thank you for being the wonderful lady that you are! You are the star of my show, and the one with the patience of Job! Now, about those DIY jobs you wanted me to do....!

Table of Contents

Note: There are two volumes in this thesis. Volume 1 contains the text of all of the Thesis Chapters, and one Appendix. Volume 2 contains the Quality Risk Management methodology and the Training & User's Manual on the methodology.

Volume 1

List of Case Studies discussed in Volume 1 of this Thesis

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List of Figures in Volume 1 of this Thesis

The Abbreviations used in this Thesis

The following abbreviations have been used in this thesis. The meaning of each is explained in the text or in the notes when it is first used.

API	Active Pharmaceutical Ingredient
CCF	Common Cause Failure
CDER	Centre for Drug Evaluation & Research
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CMC	Chemistry, Manufacturing & Controls
CPMP	Committee for Proprietary Medicinal Products
CPP	Critical Process Parameter
DIT	Dublin Institute of Technology
EEA	European Economic Area
EMEA	European Agency for the Evaluation of Medicines
ETA	Event Tree Analysis
EU	European Union
EWG	Expert Working Group
FBC	Faster, Better, Cheaper
FDA	Food & Drug Administration
FD&C	Food, Drug & Cosmetic
FMEA	Failure Modes and Effects Analysis
FMECA	Failure Modes, Effects and Criticality Analysis
FTA	Fault Tree Analysis
GAMP	Good Automated Manufacturing Practice
GMP	Good Manufacturing Practices
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard and Operability Studies
HDPE	High Density Polyethylene
HMA	Heads of Medicines Agencies
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)

ICH Q9	The ICH Guideline titled *Quality Risk Management*
ICP-MS	Inductively Coupled Plasma- Maas Spectroscopy
IEC	International Electrotechnical Commission
ISPE	International Society of Pharmaceutical Engineering
ISO	International Organization for Standardization
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
IMB	Irish Medicines Board
LLIS	Lessons Learned Information System
MA	Marketing Authorisation
MCO	Mars Climate Orbiter
MHLW	Ministry of Health, Labour & Welfare, (Japan)
MHRA	Medicines & Healthcare Products Regulatory Agency (UK)
MLD	Master Logic Diagrams
NASA	National Aeronautics and Space Administration
NUREG	US Nuclear Regulatory Commission Regulation
NRC	Nuclear Regulatory Commission
NSAI	National Standards Authority of Ireland
OMCL	Official Medicines Control Laboratory
PCI	PharmaChemical Ireland
PDA	Parenteral Drug Association
PHA	Preliminary Hazard Analysis
PhRMA	Pharmaceutical Research & Manufactures of America
Ph. Eur.	European Pharmacopoeia
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PRA	Probabilistic Risk Assessment (sometimes referred to as Probabilistic Risk Analysis)
PQ	Performance Qualification
PV	Process Validation
QP	Qualified Person
QMS	Quality Management System
QRM	Quality Risk Management
R-BAM	Risk Based Acquisition Management
RSS	Reactor Safety Study
VMP	Validation Master Plan

List of Publications arising from this Research Work

- O'Donnell, K., Greene, A., *A Risk Management solution designed to facilitate risk-based Qualification, Validation & Change Control activities within GMP and Pharmaceutical Regulatory Compliance Environments in the EU, Part I*, **Journal of GXP Compliance**, Vol. 10, No. 4, July 2006

- O'Donnell, K., Greene, A., *A Risk Management solution designed to facilitate risk-based Qualification, Validation & Change Control activities within GMP and Pharmaceutical Regulatory Compliance Environments in the EU, Part II*, **Journal of GXP Compliance**, Vol. 10, No. 4, July 2006

- O'Donnell, K., Greene, A., Failure Modes - Simple Strategies for improving qualitative Quality Risk Management exercises during Qualification, Validation and Change Control Activities, **Journal of Validation Technology**, Vol. 13, No. 2, February 2007

Note concerning other publications:

Paper's 1 & 2 above were re-published in the UK Journal titled *GMP Review* in 2007. This was at the request of the editor of that Journal, who wished to ensure that its European readers would have access to the articles, if they did not have access to the US Journal of GXP Compliance. The references for those GMP Review articles are as follows:

- *O'Donnell, K., Greene, A., A Risk Management solution for GMP Qualification, Validation & Change Control Activities, Part I, GMP Review, pp 11-17, Vol. 5, No. 4, January 2007*

- *O'Donnell, K., Greene, A., A Risk Management solution designed to facilitate risk-based Qualification, Validation & Change Control activities within GMP and Regulatory Compliance Environments in the EU, Part II, GMP Review, pp 12-16, Vol. 6, No. 1, April 2007*

Chapter 1

Introduction

1.1 Risk Management in the Pharmaceutical Industry

The management of risks associated with the use of medicinal products has been an on-going societal concern for many decades. As a concept, risk has been extensively studied in a wide range of industries and areas, and in the pharmaceutical industry, the potential risks posed by medicinal products to patients and animals are the basis for the extensive regulatory controls that govern that industry in many parts of the world.

As discussed later in this Chapter, in the section titled *Literature Review,* there have been various definitions of risk documented in the literature to date. These include definitions that present risk as something both positive and negative, where risk is associated with upside opportunity, as well as with loss and negative outcomes. In the field of medicines, risk is usually considered to be the opposite of that which delivers benefit, and this has resulted in the so called risk-benefit ratio of a particular pharmaceutical product.

Beginning in the 1930s, formal legislative and regulatory requirements in relation to medicinal products have been introduced in many countries. This reflected governmental efforts to reduce and manage the risks associated with the development, manufacture, marketing, distribution and use of medicines.

The 'Elixir of Sulfanilimide' tragedy of 1937, for example, which resulted in the death of 107 people in the United States as a result of the presence of diethylene glycol in a cough medicine (1, 2), was the driving force behind the passage of the milestone Federal Food, Drug & Cosmetic Act in the United States one year later (3). This Act was designed to reduce the risks associated with medicinal products, by setting out safety testing requirements for such products prior to their marketing in the US.

In Europe (and elsewhere), the thalidomide disaster of the 1960s was the catalyst for increased regulation of the pharmaceutical industry there (1, 4). Thalidomide not only galvanised public opinion on drug safety, it also highlighted the advantages of having a product registration system in place as the US had.

In 1960, before thalidomide was known to be teratogenic, the US Food and Drug Administration (FDA) was assessing a New Drug Application submitted by the Richardson-Merrell Pharmaceutical Company of Cincinnati, Ohio, to market a thalidomide drug product called Kevadon (4) for the treatment of morning sickness in pregnant women. Issues were identified with the short duration of the chronic toxicity studies performed on the product (4); FDA also had concerns over the absorption and excretion data submitted on the product as well as with the company's manufacturing controls (4). In late 1960, with the product still undergoing assessment in the US, cases of paraesthesia[1] were reported in the British Medical Journal for patients who had been prescribed thalidomide for relatively long periods of time, up to two years (5). The FDA suspected that a drug that could damage nerves, as it had in the paraesthesia cases seen in Britain, might also affect a developing foetus (4). This was confirmed a short time later, when cases of infant deformities began to be reported in Europe. An estimated 10,000 cases of infant deformities were eventually linked to thalidomide use in 46 countries (1, 4).

The independent assessment of medicinal products before they are allowed on the market is an example of a risk management strategy designed to ensure that only safe, efficacious and quality medicinal products are approved for marketing. The independent inspection and licensing of manufacturers of medicinal products by competent authorities is a manifestation of risk management activities also. This is because such inspections are intended to ensure that there are adequate quality systems and manufacturing controls in place that provide assurance in the quality of the medicinal products manufactured at the premises inspected.

The increasing value placed on public health, and the demand for high quality, safe and effective medicines, have driven the development of these and other regulatory systems. This is demonstrated not only by the breath of pharmaceutical legislation and associated regulatory requirements that are in place today governing the pharmaceutical industry, but also by the extent of public scrutiny that the regulators of this industry are subjected to. In addition, over recent years, there has been an intensified emphasis on the need to consider and manage risk when manufacturing and regulating medicinal products.

[1] Paraesthesia is a condition commonly associated with peripheral neuritis, a painful tingling of the arms and feet.

Three main events have contributed to this drive towards a more risk-based approach. These are described below.

1.1.1 Annex 15 to the EU GMP Guide

In Europe, the regulatory requirements governing the manufacture of medicinal products were extended with the addition of explicit risk-based GMP provisions in 2001 (6). GMP stands for Good Manufacturing Practice. It is concerned with both the production and quality control of medicinal products, and it is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use, and as required by the Marketing Authorisation or product specification (6).

General risk-based considerations have been a feature of the European GMP framework since the inception of the first version of the EU GMP Guide in 1989. For example, Chapter 1 of the EU GMP Guide, first published in 1989, stated that the holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation and do not place patients at risk due to inadequate safety (6). However, until 2001, the EU GMP provisions in relation to risk were generally of a high level, were non-specific and were somewhat aspirational in nature. With Annex 15, for the first time manufacturers were formally required to assess and analyse risk during the key manufacturing-related activities of validation and change control respectively (6).

Annex 15 was specifically concerned with Qualification and Validation activities, and it stated that a "risk assessment approach should be used to determine the scope and extent of validation", and that the likely impact of changes "should be evaluated, including risk analysis." (6)

1.1.2 The 'Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach' initiative by FDA in 2002

In August 2002 in the US, the FDA announced an initiative titled 'Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach' (7). This signalled a strong move

towards more risk-based work-practices at the FDA, and in the FDA's regulation of pharmaceutical products and their associated companies. The FDA described this initiative as a "science and risk-based approach to product quality regulation incorporating an integrated quality systems approach" (7). It was designed to allow the FDA to incorporate into its work activities "the most up-to-date concepts of risk management and quality systems approaches while continuing to ensure product quality", and to ensure that "FDA resources are used most effectively and efficiently to address the most significant health risks." (7)

This initiative was far reaching. By 2004, it had resulted in a programme of reorganisation of work activities at the FDA, which was still ongoing at the time of writing this thesis (8). A new framework for the regulatory oversight of manufacturing activities and product quality is being developed by the FDA, one that is based on quality systems and risk management approaches. The FDA has stated that its findings from the above 21st century initiative have put the Agency "on a path to restructure its oversight of pharmaceutical quality regulation, thereby developing the product quality regulatory system of the future (8)." A number of guiding principles were adopted by the FDA as part of this restructuring work, one of which was termed "risk-based orientation" (8).

1.1.3 The ICH Guideline titled Quality Risk Management, (ICH Q9)

At a more global level, in November 2005, a guideline titled *Quality Risk Management* (9) was finalised and published by the organisation known as ICH. This was important, as it was the first detailed regulatory guidance document addressing the application of Quality Risk Management principles and tools in both pharmaceutical regulatory and pharmaceutical industrial environments. This guideline was numbered ICH Q9, and is available at www.ich.org. (A general overview of ICH and its work activities is presented below, because of the importance the ICH Q9 Guideline has for this research work.)

ICH stands for the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. It is an organisation that had its beginnings at a World Health Organisation-sponsored conference of drug

regulatory authorities in Paris in 1989, at which the need for more harmonised requirements in drug regulation was highlighted (10). In April 1990, a meeting took place in Brussels between the regulatory agencies and industry associations of Europe, Japan and the United States, to plan an international conference. It was there that ICH was conceived in a formal sense (10).

ICH was a project that brought together the regulatory authorities of Japan, Europe and the United States, as well as experts from the pharmaceutical industry in those three regions. Its aims were to discuss the scientific and technical aspects of drug product registration and related regulatory requirements. Its purpose was "to make recommendations on ways to achieve harmonisation in the interpretation and application of technical guidelines and requirements for product registration (10)". A main goal of ICH was to reduce the need for duplication in clinical, animal and other testing carried out during the research and development of new medicines, whilst maintaining safeguards on quality, safety and efficacy. The objective of such harmonisation was a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines (10).

An ICH Steering Committee was formed at the initial meeting in April 1990, comprising of the six ICH co-founders (listed below), three observers (the World Health Organisation, the European Free Trade Area (EFTA) and Canada) and the International Federation of Pharmaceutical Manufacturers Association (IFPMA), which runs the ICH Secretariat and provides logistical support for ICH meetings (10).

The six ICH co-founders were:

- The European Commission/European Union (EC/EU)
- The European Federation of Pharmaceutical Industries and Associations (EFPIA)
- The Ministry of Health, Labour and Welfare, Japan (MHLW)
- The Japan Pharmaceutical Manufacturers Association (JPMA)
- The US Food & Drug Administration (FDA)
- The Pharmaceutical Research and Manufacturers of America (PhRMA)

The first international conference (called ICH1) was held in Brussels in 1991, where three workshops were held on eleven topics concerning the Quality, Safety and Efficacy of drug products. (Quality, Safety and Efficacy were chosen as the broad subjects of the conference because they reflect the main criteria which form the basis of approving new medicinal products.) The initial topics selected for harmonisation by the ICH Steering Committee have since been further subdivided and defined. The single Quality topic Specifications, for example, has since been divided into more manageable topics on Analytical Validation and Impurities, and these were further subdivided again (10). Since the first meeting, ICH has evolved into an on-going process rather than a series of conferences, and the name ICH has now become more associated with the process of harmonisation rather than with the actual conferences (10).

ICH operates on three basic principles:

- The development of scientific consensus through discussion between regulatory and industry experts;
- A wide consultation of the draft consensus documents, through normal regulatory channels, before a harmonised text is adopted;
- Commitment by regulatory parties to implement the ICH harmonised texts (10).

ICH works to a five step process, (Consensus Building, Regulatory Action, Regulatory Consultation, Adoption of a Tripartite[2], Harmonised Text & Implementation), and the tangible outcome of ICH work on any one topic is usually the publication of a guideline which sets out harmonised guidance or requirements in relation to the topic of interest across all three ICH regions - Europe, Japan and the United States (10).

ICH Q9 was a significant milestone in the development of Quality Risk Management activities within the pharmaceutical regulatory and industrial environments. It presented guidance for manufacturers and regulators on how the application of Quality Risk Management principles and methodologies may enable more effective and consistent risk-based decisions, to help ensure the availability of high quality medicinal

[2] In an ICH context, the word *Tripartite* refers to the three parts or areas making up the ICH region as a whole – Europe (as in the EU), Japan and the United States.

products for patients. It promoted, in an official, transparent manner the use of Quality Risk Management concepts, principles and methodologies within the industrial and regulatory environment (9).

ICH Q9 also presented potential mechanisms for regulatory flexibility and risk-based decision-making. Some real examples of this are being seen at the present time, including the FDA's risk-based inspection planning activities (8), and the EMEA's proposed approach to dealing with non-compliance issues with the marketing authorisation (11), which is discussed in more detail in Chapter 8 of this thesis.

Importantly, ICH Q9 is part of a wider ICH initiative (known as ICH Q8/Q9/Q10) aimed at promoting wide-ranging changes in the pharmaceutical regulatory environment across the ICH region. This initiative, manifested by a set of three ICH Guideline documents, (on Pharmaceutical Development, Quality Risk Management, and Pharmaceutical Quality Systems) represented a definite move towards more risk-based and risk-informed regulation of pharmaceuticals, with an emphasis on science-based product development and more tailored Quality Management Systems for pharmaceutical environments. This initiative is currently resulting in the development of more workable variation and post-approval change regulations, in better process understanding via the use of Process Analytical Technologies, and in Quality Risk Management activities (10).

1.1.4 The Implications of these Initiatives for Manufactures of Medicinal Products in the EU

The implications of the aforementioned initiatives and their related regulatory requirements for manufacturers of pharmaceutical products have been the subject of much discussion between regulators and industry in recent years (12, 13, 14). As a regulatory agency, for example, the Irish Medicines Board (IMB) has received numerous requests from Industry for specific guidance in the area of Quality Risk Management. While ICH Q9 has been a useful starting point for work in this area, it can reasonably be regarded as a fairly high-level and conceptual guidance document, offering guidance on the principles of Quality Risk Management without providing any

detailed or practical guidance on the application of any specific Quality Risk Management methodology within GMP environments.

The IMB had been identifying Quality Risk Management-related deficiencies during GMP inspections, and pharmaceutical manufacturing companies had on several occasions expressed an opinion to the IMB that additional regulatory guidance was required by Industry, in order to comply with the aforementioned risk-based requirements of Annex 15.

In the author's experience as a GMP inspector in the EU, informal approaches to Risk Management and Quality Risk Management have been utilised for a considerable period of time by pharmaceutical manufacturers, and this includes during qualification, validation and change control activities. However, it is evident that there is currently a general move towards the use of more *formalised* Quality Risk Management approaches for these and other activities within GMP environments (13-17). The increase in the use of formalised Risk Management tools and approaches has probably been accelerated by a number of developments, including, the guidance presented in ICH Q9 (9) on formal Quality Risk Management tools, and the higher focus which GMP inspectors are nowadays giving to Quality Risk Management activities within pharmaceutical companies (13, 18, 19). In addition, the promotion of more systematic and rigorous approaches to Quality Risk Management by regulatory agencies such as FDA (7) has been a significant driving factor.

1.2 The EU Legal and Regulatory Requirements for Quality Risk Management in Pharmaceutical Manufacturing

In the EU, the Good Manufacturing Practice (GMP) guidelines, as defined by the European Commission Directives 2003/94/EC (20) and 91/412/EEC (21), set out specific minimum requirements to be met by manufacturers in relation to the manufacture of medicinal products. These EU Directives contained provisions pertaining to Quality Management, Personnel, Facilities, Production, Quality Control, Self-Inspection and other activities relevant to the manufacturer of medicinal products and investigational medicinal products.

The Directives were given legal standing across the EU by means of their transposition in national regulations. In Ireland, for example, this was achieved with the signing into law of Statutory Instrument No. 539 of 2007, governing the manufacture of human medicinal products (22), and Statutory Instrument No. 144 of 2007, governing the manufacture of veterinary medicinal products and other animal remedies (23). These national regulations set out the legal requirement for manufactures to comply with the provisions of the Good Manufacturing Practice provisions as set out in the EU Guide to GMP.

In addition to EC Directives 2003/94/EC and 91/412/EEC, two other EC Directives contain important provisions for manufacturers of medicinal products. EC Directive 2001/83/EC (24) relates to medicinal products for human use, and this contains provisions governing the need for a manufacturer to hold a manufacturing authorisation (Article 40), to have at least one Qualified Person (QP) at his disposal (Article 41), and to use as starting materials only active substances that have been manufactured in accordance with the EC Guidelines in GMP for starting materials (Article 46). This Directive also sets out the minimum educational and qualification requirements for Qualified Persons, and addresses other areas such as how batches of medicinal products are to be certified before release by a Qualified Person. In relation to veterinary medicinal products, EC Directive 2001/82/EC (25) is similar to the human medicines directive in its provisions relating to manufacturing and importation.

The EC Guide to Good Manufacturing Practice (6) provides detailed guidance in relation to the aforementioned GMP requirements. It is structured in two Parts; Part 1, divided into nine chapters, provides guidance on the basic GMP requirements for Medicinal Products, and Part II, containing 19 sub-sections, provides guidance on the Basic Requirements for Active Substances used as Starting Materials. There are also a number of Annexes to the EU Guide to GMP. These are numbered 1 through 19, and present guidance on areas such as the Manufacture of sterile medicinal products (Annex 1), the use of ionising radiation in the manufacture of medicinal products (Annex 12), and on reference and retention samples (Annex 19).

There are no explicit references to *Quality Risk Management* in the EC Guide to GMP at the time of writing (December 2007). There are however many references to risk throughout the EC Guide to GMP (6). For example:

- Chapter 2 of the Guide, in relation to Personnel, states that "the responsibilities placed on any one individual should not be so extensive as to present any risk to quality (Ref. Paragraph 2.1, Chapter 2)."

- Chapter 5, on Production, states that "cross contamination should be avoided by….. minimising the risk of contamination caused by re-circulation or re-entry of untreated or insufficiently treated air (Ref. Paragraph 5.19, Chapter 5)."

- Annex 2, in relation to the manufacture of Biological Medicinal Products for Human Use, states that "in virus inactivation or removal processes, measures should be taken to avoid the risk of recontamination of treated products by non-treated products (Ref. Paragraph 39, Annex 2)."

- Annex 17, on Parametric Release, states that "a risk analysis of the sterility assurance system focussed on an evaluation of releasing non-sterilised products should be performed (Ref. Paragraph 3.7, Annex 17)."

As stated above, the finalisation of Annex 15 to the EC Guide to Good Manufacturing Practice for the first time set out specific risk-related guidance for manufactures in the areas of qualification, validation and change control. The Annex stated that a "risk assessment approach should be used to determine the scope and extent of validation", and that the likely impact of changes "should be evaluated, including risk analysis (6)." These GMP requirements place specific obligations on manufacturers of medicinal products and investigational medicinal products to implement risk-based qualification, validation & change control programmes.

ICH Q9 provided regulatory guidance on the potential uses of Quality Risk Management principles and tools by industry and regulators. In the area of Change Control, for example, it states that Quality Risk Management may be used to "evaluate

the impact of the changes on the availability of the final product", and to "determine appropriate actions preceding the implementation of a change, e.g. additional testing, (re)qualification, (re)validation or communication with regulators (9)." With respect to the application of Quality Risk Management principles to Facilities, Equipment and Utilities, ICH Q9 states that Quality Risk Management may be used "to determine the scope and extent of qualification of facilities, buildings and production equipment and/or laboratory instruments (including proper calibration methods) (9)." In the area of Production, ICH Q9 indicates that Quality Risk Management may be useful when determining the "scope and extent of verification, qualification and validation activities, (e.g. analytical methods, processes, equipment and cleaning methods) (9)."

1.3 Current Problem Issues in relation to the use of Quality Risk Management in Pharmaceutical Manufacturing

Quality Risk Management is not a new area of activity for EU GMP environments. As mentioned above, informal Quality Risk Management-related activities have been taking place for many years within GMP-regulated companies, even before the addition of Annex 15 to the EC GMP Guide. For example, current deviation and change control procedures can be considered to be elements of a Quality Risk Management programme at a manufacturing site, as the use of these formal procedures acknowledges the risks that may be introduced when deviations from approved procedures occur, and when changes are implemented.

Other examples include self-inspection, supplier approval, and warehouse temperature mapping activities at manufacturers. These are elements of a Quality Risk Management programme because they are carried out in recognition of the risks that may be presented by a) non-compliances with Quality System procedures, b) the use of materials from unapproved suppliers, and c) the storage of materials in environments which may be hazardous to the material or product being stored in that warehouse.

With respect to qualification and validation activities, from the author's experience as a GMP Inspector in the EU, it is evident that risk factors are often taken into account by pharmaceutical companies when designing qualification and validation programmes,

and when planning what qualification and validation work will be carried out in the first place.

However, from a review of the literature, it is evident that the application of formal Quality Risk Management methodologies across the GMP environment has been somewhat limited to date. The literature shows that some areas, especially process validation (19, 14, 26-30, 31-35), have been subjected to a higher degree of formal Quality Risk Management-related activities than other areas, such as supplier qualification, documentation, quality defects, calibration, preventative maintenance, and change control activities. There is also evidence that, despite ever increasing expenditure on qualification and validation activities (37-39), defective and non-compliant medicinal products continue to be manufactured and released. For example, there have been numerous and serious product recalls in Ireland and elsewhere over recent years (40, 41) for Quality Defect reasons relating to manufacturing activities.

As discussed in ISPE's White Paper on Risk-Based Qualification for the 21st Century (37), qualification practices are often document-intensive, expensive and time-consuming, but do not necessarily add value, or lead to clear patient-risk mitigation strategies or process understanding. Likewise, while validation activities are becoming increasingly expensive, they sometimes do not adequately address the critical aspects of processes (42). In the area of change control, planned changes often involve substantial capital expenditure, large project teams and a significant use of resource, but they can sometimes fail to identify important patient risks which are introduced by the change, and as a result, defective and harmful medicinal products do get manufactured and released (40). The ISPE's White Paper recommended that more attention should be paid to defining and controlling process-based user requirements for the item of interest, and that these then should be the main focus of qualification efforts. It also recommended that Risk Management principles should be used to determine those aspects which can directly affect product quality, and the resulting risk control mechanisms would be the focus of formal qualification work (37).

As acknowledged in ICH Q9, the use of Risk Management in the pharmaceutical industry has, to date, been limited, and the full benefits of Risk Management, as a valuable component within a pharmaceutical quality system, have yet to be realised. As

indicated above, there are currently no explicit references to *Quality Risk Management* in the EC Guide to GMP at the time of writing (December 2007), and the relevant EU Directives do not set out any definitive requirements for the use of formal Quality Risk Management principles or methodologies in GMP environments. There is on-going discussion, however, within European and other regulatory bodies responsible for monitoring compliance with GMP on how ICH Q9 might be incorporated into the regulatory framework for manufacturers (14).

In contrast, other areas within the pharmaceutical regulatory environment are at more advanced stages in their application of formal Risk Management approaches. With respect to pharmacovigilance activities on human medicinal products, for example, the formal application of Risk Management methodologies and formal planning for risk-related events are now firmly established within the European regulatory framework. This was achieved via Article 8 (3)(ia) of EC Directive 2001/83/EC (24). This Article sets out a specific requirement for the applicant of a Marketing Authorisation to submit a detailed description of the "risk-management system" that the applicant will introduce, should the Marketing Authorisation be granted (24). In addition, and in order to assist pharmaceutical companies in complying with this Article 8 provision, the EMEA's Committee for Medicinal Products for Human Use (CHMP) published, in November 2005, detailed practical guidance for Marketing Authorisation Holder companies on setting up and implementing Risk Management systems in relation to medicinal products for human use (43).

In relation to manufacturing activities for medicinal products, when one compares the current level of application of formal Quality Risk Management methodologies in the pharmaceutical manufacturing industry with that of other manufacturing industries, such as the automotive and semi-conductor manufacturing industries, it becomes evident that the pharmaceutical manufacturing industry has a long way to go to achieve a similar state of knowledge about risks and their contributing factors.

In the semi-conductor field, for example, a high focus is placed on the importance of process and product reliability (44). This has resulted in a high degree of process understanding and a detailed knowledge about the causative pathways that can lead to important failure modes, such as the build-up of electrostatic discharge on semi-

conductors. This is indicative of the extent to which Quality Risk Management methodologies have been applied in that industry as a means to better process understanding and risk control (44). The pharmaceutical manufacturing industry is not at this same level of advancement in its application of formal Quality Risk Management at this time.

1.4 The need for a formal Quality Risk Management methodology specifically designed for facilitating risk-based qualification, validation and change control activities within GMP environments

There are many formal Quality Risk Management tools available that may be applied in the pharmaceutical manufacturing environment (9). These include methodologies such as Fault Tree Analysis (45), Failure Modes and Effects Analysis (FMEA) (46, 47), Failure Modes, Effects and Criticality Analysis (FMECA) (47), Hazard Analysis and Critical Control Points (HACCP) (48, 49), among others (50).

These methodologies have been extensively described and reviewed in the literature, and examples of their application within GMP and other environments are also described (e.g. see 16-17, 19, 26-28, 44-64).

None of these tools, however, was specifically designed for GMP applications, much less as solutions for facilitating risk-based qualification, validation and change control activities within GMP environments. In the author's experience, when using such tools for these purposes, it can often be unclear how risk-related qualification and validation requirements may be identified from the outputs of exercises carried out using such tools, and as a result, a degree of design modification is often required before an existing tool may be used for such activities.

In addition, aspects of some existing Quality Risk Management tools can be considered problematic from a regulatory GMP perspective. For example:

- The role played by GMP controls during risk estimation, risk mitigation and risk control activities is often not adequately addressed by existing tools such as FMEA, HACCP and FTA. During risk estimation activities, for example, most applications

of FMEA-based methodologies (14, 26, 46-47, 56), as described by Stamatis (44) and others (51), do not involve any formal consideration of the controls that may affect the severity of the effects of a failure mode before that failure mode is assigned a Severity rating for those effects. This is also the case following risk control activities with FMEA-based methodologies, when the Severity rating for a failure mode is being re-assessed. (The emphasis is often on detection-type controls). With respect to Fault Tree Analysis methodologies (45), there is usually no formal or documented consideration given to how the controls, that may currently be in place, may affect or reduce the risk presented by the fault being considered.

- The use of Risk Priority Numbers (RPNs) in FMEA & FMECA-based Quality Risk Management tools, as a means to determine which risks are to be mitigated and which are not, is often lacking in rigor and scientific basis (e.g. 26, 46-47, 65). For example, the selection of a specific RPN cut-off number is often lacking a clear rationale, with no consideration being given to the confidence levels that may be associated with the RPN threshold value selected. In addition, the generation of RPN numbers by the multiplication of three ordinal scale numbers, is, as discussed by Kmenta and Ishii, among others, (52-54), not a mathematically valid operation.

- The way detection is dealt with in some tools is contrary to one of the fundamental GMP principles, that of *assuring quality* rather than relying on *testing-in quality* via detection-type tests. Improving the detectability of a failure mode or negative event is useful, but as McDermott et al point out (51), this is often costly and does not improve the quality of the product manufactured. Some tools, such as the GAMP 4 Risk Assessment methodology (55), allow for a risk to be considered mitigated or under control when a high detection rating can be assigned to the risk in question. In GMP environments, it is not normally acceptable to place such a high reliance upon detection-type controls in the absence of an adequate level of assurance in the manufacturing process that leads to the finished product. (In the author's opinion, there is currently an opportunity with the Quality by Design, Design Space and PAT-based initiatives of ICH and FDA, via ICH Q8 and ICH Q9, and FDA's PAT initiatives, (10, 66) to move away from such a high reliance upon end-product or

end-process detection type testing, and to move towards increased process understanding and process control, and current RM tools do not really facilitate this.)

- The linking of the outcomes of Risk Assessment exercises with qualification & validation activities is an area that is currently not well addressed in many existing tools. For example, with methodologies such as Preliminary Hazard Analysis (PHA) (9, 50) and Hazard and Operability Studies (HAZOP) (9, 50, 63), there is no formal requirement to identify qualification and validation requirements for controls relevant to the risks in question, and there is no provision made in their methodologies to identify and document critical process parameters for such controls.

Of the tools which are GMP-specific, such as the approaches developed by ISPE (67) and GAMP (55), their focus tends to be somewhat narrow, being tailored for equipment/systems qualification and computerised systems validation, respectively. As a result, the day-to-day practicalities of how to apply Quality Risk Management more broadly remain somewhat under-developed.

In addition, of the tools available to date, few, if any, were designed to serve as a complete, documented and ready-to-use Quality Risk Management solution for facilitating risk-based qualification, validation & change control activities across a broad range of GMP areas, incorporating all of the components of Quality Risk Management which have been accepted via ICH Q9 as being important (9). These are: Risk Assessment, Risk Control, Risk Communication and Risk Review. FTA methodologies, for example, are not designed to deal with risk communication and periodic review activities (45), and HACCP applications often do not always require any estimation of the risks associated with individual hazards (48-49).
From discussions in July 2007 between the author and other GMP Inspectors working in the EU and elsewhere, it was evident that a significant and widespread issue for GMP inspectors concerning the application of Quality Risk Management in GMP-regulated environments was the fact that Risk Assessment activities often carried out in response to production and quality problems during manufacturing were being regarded as

Quality Risk Management activities, when in fact they represented only part of the overall Quality Risk Management process (14).

In this regard also, it is evident from a review of currently available Quality Risk Management methodologies that some of the activities associated with Quality Risk Management exercises are currently under-developed. These include:

- Brainstorming activities (e.g. for identifying and documenting potential Failure Modes & their causes, and for estimating Risks)
- Dealing with disagreements in opinion during Quality Risk Management exercises
- Performing Risk Communication activities
- Performing Periodic Review activities

This means that documented procedures or guidance are often unavailable when performing such activities within GMP environments. This is problematic from a GMP perspective.

In addition, many existing Quality Risk Management tools do not adequately deal with the problems of subjectivity and uncertainty which often arise during Quality Risk Management work, and most tools do not provide any strategies for addressing such problems during the application of Quality Risk Management in GMP or other environments. For example, there is often no documented means or clear guidance in place for performing certain activities (such as brainstorming) which are susceptible to problems of subjectivity and uncertainty when using a Quality Risk Management tool to identify and document potential failure modes, their probabilities of occurrence and their causes (e.g. 9, 26, 29-31, 45-49, 55, 67-68). The learnings gained from the many years of detailed and peer-reviewed research into human cognitive and behavioural processes when humans are performing activities such as brainstorming or when humans are providing opinions on issues such as probability estimates are often not taken into account in existing Quality Risk Management methodologies.

If the full benefits of ICH Q9 are to be realised in the pharmaceutical manufacturing environment, particularly with respect to qualification, validation and change control

activities, it is likely that the availability of more formalised and scientific approaches to Quality Risk Management in GMP environments will prove beneficial. These should be specifically designed for GMP environments and their related applications. In addition, it is not unreasonable to expect efforts to be made at GMP Inspector level within the EU that promote compliance with the risk-based requirements of Annex 15, by providing detailed and practical guidance on ways in which Quality Risk Management might be applied within GMP environments. This research work is an attempt to do just that.

1.5 Literature Review

1.5.1 Risk Concepts & Definitions

In recent years, the management of risks has become a major public concern across a wide spectrum of activities. The environment in which we live is affected by hazards of various kinds, such as man-made pollution and the depletion of natural resources.

Nivolianitou (69), in a review of the development of risk-based legislation in the European Union, explains that, while modern societies have become healthier and safer on average, "the public has become more and more concerned about risks of all kinds, both natural and man-made." Therefore, when events such as major industrial accidents occur, governments and other public bodies respond by passing laws such as the Seveso Directive of 1982 (70-71), which attempted to address the risks posed by such accidents.

The body known as the 9-11 Commission, (*full name - The National Commission on Terrorist Attacks Upon the United States*), made several recommendations in relation to how specific risks relating to terrorist activities might be managed (72). For example, the Commission recommended that federal funding to US states and cities for emergency preparedness "should be based solely on risks and vulnerabilities", putting New York City and Washington, D.C., at the top of the current (July 2004) list. It also recommended that the U.S. border security system should be based on personnel screening activities focussed on identifying "particular, identifiable suspects or

indicators of risk", rather than a system that involves "guesswork about who might be dangerous" (72).

Risk is usually considered to be made up of two components, chance and consequence. In ISO/IEC Guide No. 51:1999, titled 'Safety aspects - Guidelines for their inclusion in standards', risk is defined as the "combination of the probability of occurrence of harm and the severity of that harm (73)". ICH Q9 uses this definition of risk (9).

The origins of the word 'risk' are unclear. Vesper, in his outline of the historical development of risk-based concepts and thinking, discusses how the word risk has its origins in the 17th century French word *risqué*, meaning *danger, in which there is an element of chance* (50). Shattel (74) explains that originally, the concept of risk was used primarily to describe a loss or hazard to the person, and in the early 18th Century, the commercial loss of insured property and goods was the primary focus of risk considerations.

The current edition of the Oxford Dictionary of English (75), states that the word risk originated in the Italian word *risco*, meaning danger. It defines risk, when used as a noun, as a situation involving exposure to danger, and the possibility that something unpleasant will happen. As a verb, the word risk means to expose one to danger or loss (75).

NASA, an organisation which spends considerable resources on reducing and controlling risk associated with the hazards inherent in space exploration, uses two definitions of risk; in general terms, risk is considered to be the "uncertainty associated with the realization of a non-certain outcome (56)". With respect to safety and systems, NASA defines risk as the frequency and severity of an undesired occurrence/consequence (56).

This is expressed mathematically at NASA as shown in Figure 1.1, below, and graphically, risk curves can be generated showing the relationship between frequency and consequence.

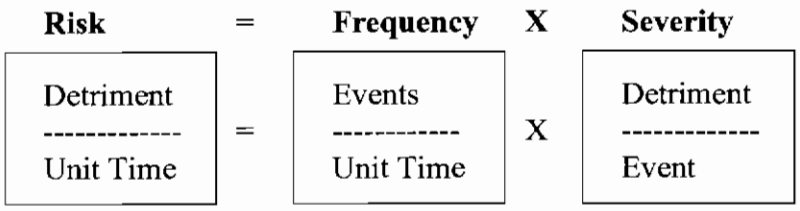

Figure 1.1: NASA's expression of Risk (56)

Key to any considerations of risk are the terms harm and hazard. In ICH Q9, harm is defined as "damage to health, including the damage that can occur from loss of product quality or availability (9)". A hazard is defined in ICH Q9 to be a "potential source of harm", a definition again taken from ISO/IEC Guide 51:1999 (73).

In a simple but elegant discussion of risk and its definitions, Kaplan and Garrick (77) define risk as the "possibility of loss or injury" and "the degree of probability of such loss". They discuss how a hazard "simply exists as a source" of such loss or injury, and that "risk includes the likelihood of conversion of that source into actual delivery of loss, injury, or some form of damage." There have been many different definitions of risk documented in the literature, and these include definitions that present risk as something both positive (i.e. something associated with upside opportunity, to quote from Raz and Hillson) and negative (76).

In this work, and coupled with common practice in pharmaceutical–related areas in which risk is often considered an opposite of things which deliver benefit, (as in the so called risk-benefit ratio of a particular pharmaceutical product), risk is considered to be associated with loss, not benefit, and with danger and potential negative consequences.

One issue that often arises during Risk Management discussions is the question of whether risk can ever be considered to be zero. Some researchers are of the opinion that, while risk may sometimes be small, it is cannot be zero. Kaplan and Garrick (77), for example, express risk simply as:

$$\text{Risk} = \frac{\text{Hazards}}{\text{Safeguards}}$$

Figure 1.2: Kaplan and Garrick's Expression of Risk (77)

Kaplan and Garrick argue that, as a result, "we may make risk as small as we like by increasing the safeguards, but may never, as a matter of principle, bring it to zero (77)."

In everyday language, the concepts of risks and hazards are often confused, with the terms risk and hazard sometimes being used interchangeably. The current edition of the Oxford English dictionary acknowledges this practice, defining the word hazard as "risk, danger; a source of this (75)." The current edition of the Collins English Dictionary 21st Century, likewise defines risk as "the possibility of incurring misfortune or loss; hazard (78), and it defines a hazard as "a thing likely to cause injury." However, the concepts of hazards and risks are not the same, and most formal definitions consider a hazard to be a source of risk, but not actually a risk. While this may not pose a problem in everyday communications, in formal discussions of risk and risk management, the terms risk and hazard should not be used interchangeably, and it is important that they are clearly differentiated and understood.

1.5.2 Risk Management

ICH Q9 defines Risk Management as "the application of quality management policies, procedures, and practices to the tasks of assessing, controlling and communicating risk (9)".

The National Standards Authority of Ireland (NSAI), Ireland's official standards body by virtue of the National Standards Authority of Ireland Act, 1996, describes Risk Management as "a key business process within both the private and public sectors around the world (79)." The NSAI, in discussing the role played by effective risk management and its resulting controlled environment in corporate governance, explains

how, in response to various corporate collapses and scandals, many of the resulting legislative changes pertaining to business require effective risk management at a corporate level. One manifestation of such changes, as discussed by the NSAI, can be seen in the insurance field, where evidence of "good risk management practice is ….. increasingly being required before insurance can be obtained (79)."

There are many other official publications which offer definitions for Risk Management, and there are several Risk Management-related standards that set out the activities that are generally involved in executing Risk Management-related activities. These Standards are discussed in Section 1.5.5 below. With the publication of ICH Q9, the EU GMP manufacturing environment is principally concerned with the application of Quality Risk Management, not just Risk Management. The meaning of the term Quality Risk Management and the components which make up Quality Risk Management are reviewed in detail in the next section.

1.5.3 Quality Risk Management

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 (9)." It states that effective quality risk management can facilitate better and more informed decisions, and that it may provide regulators with greater assurance of a company's ability to deal with potential risks and may beneficially affect the extent and level of direct regulatory oversight. ICH explains how quality risk management activities can help ensure the high quality of medicinal products, by providing a proactive means to identify and control potential quality issues with the product during development and manufacturing.

ICH Q9 explains that, although a systematic approach to quality risk management is generally preferred, it is neither always appropriate nor necessary to use a formal risk management process, and that the use of informal risk management processes may also be acceptable.

ICH Q9 states that quality risk management should be integrated into existing operations of the industry and regulatory authorities, and included in existing

documentation for operations. This is an important consideration for companies and regulatory bodies starting to begin using formal quality risk management methodologies, and it is a core requirement of the EMEA *Reflection Paper on QP Discretion*, mentioned above and discussed in more detail in Chapter 8 of this thesis (11).

As explained by McDermott et al., (51), when quality risk management activities are not well integrated into the Quality Management system of the organisation, there is a danger that the data which are used during the risk assessment stage of such activities may be unreliable or unfounded, and that the risk assessment will be reduced to a mere "guessing game." In relation to the integration of the quality risk management activities into Quality Management systems, the 2004 Risk Management standard published by the organisations Standards Australia and Standards New Zealand, (80), and the Risk Management standard published by the Canadian Standards Association (81), provide detailed information and useful guidance in this area.

ICH Q9 states that quality risk management activities are usually, but not necessarily, undertaken by interdisciplinary teams dedicated to the task (9). It recommends that teams for specific quality risk management activities include expertise from the technical areas involved, as well as individuals who are knowledgeable of the quality risk management process. This interdisciplinary approach is a feature of many, but not all, quality risk management methodologies. In the nuclear power industry, for example, the application of Fault Tree Analysis as a risk management methodology has often been performed by just one analyst, albeit one who is highly knowledgeable about the item under study (82). FMEA-based methodologies, on the other hand, usually make it a requirement to have a multidisciplinary team performing the exercise (46-47). Stamatis outlines the synergistic advantages afforded by the use of multidisciplinary teams, and the factors which can influence and adversely affect team-based quality risk management exercises, such as inadequate planning, and the unequal participation of the various team members (44). See also McDermott et al, (51), for a useful discussion in this regard.

The usefulness of multidisciplinary teams in quality risk management activities is not confined to only FMEA-based methodologies. Event Tree analysis (ETA), for example,

is a Risk Management methodology in which the safety and other control systems in place for overcoming the effects of the undesirable event (called an initiating event in ETA terminology) are assessed in terms of their probabilities of success or failure (50, 82). Accident pathways are generated for different failure scenarios, and the overall probability associated with each accident pathway or scenario is determined on the basis of the individual probabilities assigned to each control mechanism success or failure event. As described by Rasmussen (82), one challenge with ETA is to "define a set of initiating events that, when fully developed, produces all the important accident sequences." This is clearly facilitated via the use of multidisciplinary teams.

Another key activity during Event Tree analysis which benefits from the use of multidisciplinary teams is when the order of placement of the individual control functions across the top of the event tree is being determined. This is important when the performance of one control system affects the performance of another control system, and it is an activity that the Nuclear Power industry has struggled with. Rasmussen (82) explains how it is essential for analysts performing Event Tree analyses to "have a detailed understanding of all plant systems and how they operate and interact with each other." Clearly, the use of multidisciplinary teams during such work is beneficial in this regard.

The guidance presented by ICH Q9 shows how, in pharmaceutical-related applications, the Quality Risk Management process can be broken down into four main core activities. These are: Risk Assessment, Risk Control, Risk Communication and Risk Review. Each of these is reviewed below in some detail.

1.5.3.1 Risk Assessment

ICH Q9 describes Risk Assessment as an activity consisting of three parts: risk identification, risk analysis and risk evaluation. Three key questions are central in this regard:

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

A fourth question not explicitly stated in ICH Q9 (but which can be inferred from the text of ICH Q9), and which, in the opinion of the author, is important during Risk Assessment activities is: "How acceptable is the estimated risk?"
Risk identification is defined in ICH Q9 as the systematic use of information to identify hazards referring to a risk question or problem description. Such information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the 'What can go wrong?' question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is defined in ICH Q9 as the estimation of the risk of the identified hazards. It is the process that focuses on the second general question, seeking the likelihood that risks identified in risk identification might 'go wrong.' It is generally regarded however that during the risk analysis stage, the third question, that in relation to consequences and severity, is also answered. The probability and severity are then usually combined to produce an estimated risk.

ICH Q9 states that during *Risk evaluation* activities, the identified and analysed risk is compared against given risk criteria. ICH Q9 explains that the output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a probability scale from 0 and 100% is used. Alternatively, ranges of risk can be expressed using qualitative descriptors, such as "high", "medium", or "low", and they should be defined in as much detail as possible. In quantitative risk assessments, a risk estimate provides the likelihood of a specific adverse consequence, given a set of risk-generating circumstances (9).

Overall, Risk Assessment is a method which identifies negative events in a process, system, programme, product, etc, and their causes. It estimates or calculates the risk associated with these negative events, it assesses that risk by comparing it against predefined risk acceptability criteria, and it determines whether a risk is considered to be acceptable or not.

Identifying potential negative events is one of the most important activities in any risk assessment process, because all of the remaining activities to be performed will

probably relate to these events. This is not just important for the use of Quality Risk Management in the pharmaceutical industry - it applies more broadly too. In his book titled 'Cases in Global Strategy', West (83) demonstrates the importance of this step in business environments. In West's business-related application of Risk Management, the process of identifying potential negative events begins with the identification of individual and specific risk factors for the business under consideration. This is so that risks can be identified and addressed, allowing particular risks to be assessed and managed. West demonstrates how taking a case by case approach to identifying potential negative events during risk management work is beneficial when trying to identify the risks which are pertinent to a specific business or company. This is because a company operating in one market under one set of specific circumstances may have quite different risk factors (and hence risks) than another company operating in a different market, characterized by a different set of circumstances.

Consider for example, a company providing media advertising services for the US market. West considers the US to be a mature market for this business activity. This market will likely become more competitive as time goes by, resulting in lower expected returns on the investments made. West argues that this sort of company will be particularly vulnerable to changes in the growth rate of the advertising market in the US, and that reductions in the growth rate will affect investment returns. Thus, in West's risk factor model, changes in market growth is an important risk factor for such a company. Market growth rates may, however, not be as important for other companies, whose risk factors may be quite different. West cites the case of a company planning an investment in an overseas market such as in Eastern Europe, where the potential for political change might be a much more important risk factor (83).

Interestingly, all of the risk factors mentioned in West's book are related to *changes*. Not only does this bring to mind Change Control, it demonstrates the importance of having adequate Change Control procedures in place, and how it is a concept not just confined to the Pharmaceutical manufacturing industry. West shows why it is useful to consider changes on a case-by-case basis, and with a specific focus on identifying the important risk factors for the case concerned (83). This is so that, from a risk management perspective, one may more fully understand the risks presented by such changes.

Identifying the likely causes of potential negative events is another key activity in any risk assessment process, and it is important that the Quality Risk Management process gives adequate attention to this area. Production processes typically involve five main components – equipment, people, methods, environment, materials and measurements (51). When the likely causes of potential negative events are being identified, it is useful if each of these areas is considered and taken into account. Ishikawa analysis, also known as fishbone analysis, is a simple but structured technique that facilitates such work (84).

There is evidence in the literature that poor design can be a highly significant causative factor for many failures. Research by Curley and Ryder in 1992 demonstrated that 76 percent of all engineering-related changes studied were intended to correct poor design features in the items under study, while only 24% related to engineering improvements (85). Thus, it is important that when the likely causes of failures or potential negative events are being identified, design-related factors be taken into account.

One of the main difficulties associated with Risk Assessment-related activities is the level of uncertainty and subjectivity that can be associated with such activities, and there are many references in the literature to the subjective and uncertain nature of Risk Assessment & Management for pharmaceutical applications and in other areas, (e.g. 9, 26-28, 46, 86-89).

Uncertainty is generally unavoidable, given the generally accepted definition of risk[3], which includes a probability factor for the occurrence of a hazard or harm. ICH Q9 also acknowledges this, listing some typical sources of uncertainty during the Risk Assessment component of Quality Risk Management activities. These include gaps in knowledge, gaps in pharmaceutical science and process understanding, and importantly for the discussion below, uncertainty in the sources of harm (e.g. failure modes of a process) (9). In many cases, unless the source of the hazard or harm is entirely eliminated, uncertainty cannot be avoided when one tries to estimate and manage resulting risks.

On discussions of natural and industrial hazards, Nivolianitou explains how difficulties in the management of those risks are "compounded by the fact that there is often great uncertainty associated with estimates of their nature (69)". She explains how such uncertainty is sometimes due to a "sparse database from which to derive risk estimates" and a poor knowledge "of the ways in which accidents, illnesses, or other forms of harm result from exposure to a technology (69)."

With respect to problems of subjectivity, this is acknowledged as an issue in many publications (e.g. 27-28, 87) including ICH Q9, which explains how "each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm (9)". A new draft ISO Standard on Risk Management (discussed further below in the Section titled *Risk Management Standards*) also highlights the problems of uncertainty that may be encountered during the assessment of risks (79). Nivolianitou explains that each party with an interest in a particular risk management activity may have "its own goals and agenda", and as "scientific experts frequently disagree on the nature of the risks", each interested party "can typically find someone to support its position (69)."

During discussions (e.g. 13-14) between the author and other European regulators over recent years on the potential application of Quality Risk Management for assisting with the planning of regulatory activities, such as market surveillance and GMP inspection programmes, the subjective and uncertain nature of Risk Assessment activities has been a common item of interest.

One of the most significant sources of uncertainty and subjectivity in Risk Assessment activities is the *probability of occurrence* factor that is often used when estimating risks. Many definitions of risk include a probability or possibility factor for hazards, but the probability of occurrence of an event is an item that has attracted much debate in the literature over the years, and its exact meaning has been a significant source of disagreement among mathematicians (89).

[3] Risk is defined in the ISO/IEC Guide 51:1999 as "the combination of the probability of occurrence of harm and the severity of that harm".

As explained by Kaplan and Garrick, "people have been arguing about the meaning of probability for at least 200 years, since the time of Laplace and Bayes (77)". Two major schools of thought have developed in this area; the so-called "frequentist" (or classical) school, and the "subjectivist" (or Bayesian) school (77). As discussed by Morgan, in the widely accepted "subjectivist" view of probability, the probability of an event is "the degree of belief that a person has that it will occur, given all of the relevant information currently known to that person (89)." Thus, probability is not only a function of the event itself, it is also dependant upon the state of information known to the person (or group) assigning the probability value (89). The *frequentists*, on the other hand, define the probability of an event's occurrence as the frequency with which it has been found to occur in a long sequence of similar trials. Here, the probability is the value to which "the long-run frequency converges as the number of trials increases (89)."

Morgan explains how this view of probability is problematic, in that "for most events of interest for real-world decision making, it is not clear what the relevant population of trials of similar events should be (89)." Rasmussen, in his useful review of probability-based risk assessment tools, gives a more comprehensive account of the differences in the two approaches (82).

As discussed in ICH Q9, risk assessment activities can involve qualitative, semi-quantitative or quantitative approaches, and there are different Quality Risk Management methodologies available which facilitate each approach. Quantitative approaches such as Probabilistic Risk Assessment (89) generally involve assigning quantitative probability of occurrence values to potential failure modes of faults. (In Chapter 7 of this thesis, a detailed discussion on such approaches is presented.) Rigorous mathematical statistical methods such as *Monte Carlo* simulation modelling may also be employed to facilitative quantitative risk assessments. A comprehensive description of this method is provided by Vose (88).

Some organisations and industries employ a combination of qualitative and quantitative approaches to risk assessment. At NASA, for example, both qualitative and quantitative methodologies are used (56, 90). Qualitative and semi-quantitative methods such as FMEA and Master Logic Diagramming are generally used first to characterise hazards

and failure modes (56). More quantitative methods such as probability-based Fault Tree Analysis are then used, "when qualitative methods do not provide an adequate understanding of failures, consequences and events (56)."

In the author's experience, it is useful to exercise caution when estimating or determining quantitative probability of occurrence values (or ratings) for a potential negative event. This is because accurate probability of occurrence values have often been difficult to obtain when the author was executing Quality Risk Management exercises on various items under study. There are several reasons for this. Firstly, probability of occurrence relates not to the effects of the potential negative event, but to the likelihood of occurrence of the actual event itself, or to its cause, and often, there are inadequate data available to determine this accurately. Secondly, some negative events may occur because of systematic or random errors, and their error rates may not be known or well understood. This was highlighted as an issue more than 25 years ago by Rasmussen, who in 1981, during a review of the application of Probabilistic Risk Assessment methodologies to the US nuclear power industry, stated that "today, the methods for estimating equipment failure probability are quite well developed" and that the "dominant contributor to the uncertainty in the results was the uncertainty in the failure rates of components and in the human error rates or operators and maintenance personnel (82)."

Thirdly, it is important to consider how probability of occurrence values are expressed during risk assessment activities. Probability of occurrence estimates are usually expressed using ordinal scales, such as a scale of 1 through 5, where a value of 1 may represent a very low probability, and where 5 may represent a very high probability.

With ordinal scales, as discussed by Conrow in 2003 and others (91, 54), the magnitude of the individual values is not meaningful in a numerical sense. For example, an event with a probability of occurrence of 4 on an ordinal scale has of course a higher probability of occurring than an event with a probability of 2, but it is not necessarily twice as likely to occur.

As explained by Kmenta and Ishii (52), it is not mathematically permissible to multiply ordinal scale values, and numerical operations such as (Risk = 3 x 4) or (Risk = 3 x 4 x

2) have questionable validity. Research in the field of cognitive psychology has found that word descriptors (e.g. high, medium, low) may be more valid than numerical descriptors, and may be preferable, because there will then not be the temptation to multiply the individual ordinal numbers to generate risk numbers (92).

In relation to the estimation of probabilities of occurrence and other parameters for which there may be some degree of uncertainty and subjectivity during Risk Assessment activities, research in the areas of human psychology and experimental psychology served as an important source of information for the author throughout this research work. The work of researchers such as Kahneman, Tversky, Fischhoff, Slovic, Starr, Keller, Litai and Lichtenstein was particularly useful in this regard (92-94, 96-98). This research in human psychology and experimental psychology was studied in order to better understand what is known about the ways in which human judgements and opinions are formed in the face of subjectivity and uncertainty. This research was considered important, because a central feature of Risk Assessment activities concerns the need to make decisions and judgement calls about problem areas and issues that are uncertain, such as the probability of an event occurring.

Important learnings were identified from the author's review of that research, and coupled with the many learnings gained when testing and evaluating this methodology during the various stages of this research work, (as discussed in Chapters 2 through 4 of this thesis), a number of practical strategies were developed and incorporated into the design and structure of this methodology, in order to address the problems of subjectivity and uncertainty that may arise during Quality Risk Management activities. The author's findings in this regard, and the aforementioned strategies, are presented and discussed in Chapter 5 of this thesis.

1.5.3.2 Risk Control

ICH Q9 describes Risk Control as a decision-making activity designed to reduce and/or accept risks. It usually occurs after Risk Assessment, and at a fundamental level, its purpose is to reduce the risk to an acceptable level.

During Risk Control activities, the following key questions are asked:

- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk Control, however, is not only concerned with the reduction of risks; it also concerns the maintenance of risks within specified levels. In GMP environments, Risk Control activities usually involve identifying controls and measures which may reduce or control the risk associated with a failure mode or negative event. Risk Control activities can serve to determine Critical Process Parameters for certain controls, how they will be monitored, and the level of Qualification & Validation which may be required, if any, for such controls.

There are many types of controls that can be considered during Risk Control activities, and it is important to note that some types of controls may be less effective than others, and may be affected by external factors and influences (50). Stamatis discusses how visual inspection-based controls have been shown to only be 79% effective in some cases, and how the effectiveness of such controls can be affected by who is performing the inspection, and by the conditions provided for the inspection (44).

Vesper categorises Risk Controls into two broad categories – controls which prevent, and controls which protect (50). Preventative controls are the better of the two options, and the focus here is on the hazard and the factors which cause it to be expressed. Vesper explains that situations can arise in which the hazard cannot be changed or its probability altered, and protection may be the only strategy available. Here, the risk is openly recognised, and risk managers take the position that there should be something done to reduce the effects of that risk.

Risk Control activities also serve to determine what detection or other controls are already in place that may maintain a risk within specified levels, and that give assurance that the risk is adequately controlled & that no further controls are required.

1.5.3.2.1 Types of Risk Control

The types of Risk Control actions that may be selected during Quality Risk Management exercises are varied, as the following examples demonstrate (44, 50, 51, 56):

- Eliminating the hazard, by re-designing the process or item in question, perhaps by replacing a component in the process with a component which does not present the same hazard. (Here, it is important that any risks presented by the new component are assessed and managed.)
- Isolating the item, process, area, etc., in which the hazard may occur, so that the impact of the effects of the hazard may be reduced and contained.
- Ensuring that effective procedures and checking activities are in place to ensure that unwanted steps and actions are avoided.
- Training operators and other staff to comply with procedures and policies.
- Designing in Redundancy / Contingency controls so that if the negative event or failure mode occurs, there are control systems in place which reduce or counteract the effects of that negative event or failure mode.
- Adding fool-proof controls which cannot be by-passed via human error or by accidental or deliberate non-compliance with procedures. (An example of such a control would be a requirement for an operator to confirm the volume of a solvent to be added to a vessel by re-entering the volume required into a computer system controlling the transfer of the solvent.) This approach is sometimes referred to as 'mistake-proofing'.
- Providing warning information to relevant people about the hazard or its potential effects. An example here is a warning on the label of an injectable product not to use the product if particulates are observed in the solution.
- Building in new & improved Detection Mechanisms, so that if the negative event or failure mode occurs, it, or its effects, may be detected in an appropriate timeframe.

- Where detection controls are important in controlling a risk, training operators to better detect the effects of the negative event or failure mode.
- For equipment-related negative events or failure modes, improving Preventative Maintenance activities so that the probability of occurrence of the negative event or failure mode may be reduced.

1.5.3.2.2 Coupling and Complexity Issues

While the above Risk Control activities are largely self-explanatory, some types of Risk Control activities are not so obvious. One such Risk Control activity is that which reduces the extent of complexity and coupling in the process or item under study. This is a Risk Control strategy which is often overlooked in existing Risk Management methodologies, but which can provide for effective risk reduction if used correctly. The following is a discussion in this regard.

Contrary to popular belief, it is not always the case that accidents can be prevented through good organisational design and management (90, 95). Normal Accident Theory suggests that, in some systems, accidents are inevitable (90). These are systems which can be described as complex and tightly coupled. The Risk Management work performed at NASA in the US has focussed much effort in understanding system complexity and coupling, and NASA's findings in this area are useful for this discussion. At NASA, complex systems are described as systems with:

- Design features such as branching and feedback loops;
- Unfamiliar, unplanned or unexpected sequences which are not visible or not immediately comprehensible;
- Opportunities for failures to jump across subsystem boundaries (90).

Tightly coupled systems are described as systems with:

- Time dependent processes that cannot wait;
- Rigidly ordered processes, (as in Sequence A must follow B);
- Where only one path has a successful outcome.

- Where there is very little slack in the system, as the system requires precise quantities of specific resources for successful operations (90).

With complex and tightly coupled systems, accidents may occur via combinations of events that are practically limitless, and "cascading failures can accelerate out of control, confounding human operators and denying them a chance of recovery (56)." NASA's has adopted two discrete strategies in order to reduce the risks presented by complex and tightly coupled systems.

The first is to increase system reliability, for example by introducing redundancy into the system so that there is a back-up system or control which can counter the effects of the failure, or by having continuous operations and effective operator training and work simulations, in order to increase compliance with approved procedures.

The second strategy involves formal efforts to better understand and reduce system complexity and coupling. In this regard, NASA promotes moving beyond the normal accident investigation pathways, which often only focus on operator error, inadequate training, faulty system design, mechanical failure, etc, towards investigations which give more attention to near-miss events, close calls, incidents and mishaps. NASA promotes closer scrutiny of these events, because the "root causes of potential major accidents can be uncovered through careful analysis" in this area, and meaningful and proper corrective actions for the prevention of future accidents can then be developed (90). NASA has found that this approach is "effective in identifying unforeseen complex interactions" in tightly coupled systems (90).

Another strategy that NASA uses to address the risk associated with system complexity and coupling is to encourage system designs that limit system complexity and coupling from the outset (90). Decoupling and reducing system complexity can be a useful risk mitigation strategy in pharmaceutical GMP environments, because manufacturing and related work processes are often multi-step, highly complex, and tightly coupled. For example, change control activities relating to packaging and artwork can be highly complex because they can require the input of several different groups and people for the co-ordination, assessment, review, approval and implementation of the proposed change, not to mention the input of regulatory agencies and off-site printing companies

as well. In addition, such activities are often tightly coupled, as there can be strict timelines to be adhered to for each part of the process, and complex interactions may have to take place in a certain order in order to allow the change to be implemented in a compliant but economically viable manner. Such interactions may include those between regulatory affairs and marketing groups, and between regulatory affairs and production personnel, in order to communicate and schedule batch manufacture with the changed packaging or labelling component.

This is an area that can be high risk for companies. In the author's experience as a GMP Inspector with the Irish Medicines Board, several non-compliances have come to light over recent years (2004-2007) in medicinal product packaging and labelling which can be attributed to the poor management of packaging and artwork change control. This has resulted in the cessation of QP batch release activities in several companies, and in market shortages of important medicines. Investigations during this time revealed that often, the procedures and systems in place at those companies for packaging and artwork change control were highly convoluted, had many interdependencies, were subjected to tight timelines, and could be described as being complex and tightly coupled. Sometimes, there was a poor understanding of how the change control system operated, and in one case, key staff involved in packaging and artwork change control activities were totally unaware of two other key groups at another location within the company that were highly involved in the implementation of such packaging and artwork related changes. It was clear that a reduction in system complexity and coupling would be of benefit.

In the pharmaceutical GMP environment, the concept of the existence of complex, tightly coupled systems is not one which is generally focussed on or well understood during Quality Risk Management activities, and there are opportunities for improvement and learnings in this area.

Current advances in Process Analytical Technology (66), and the current drive towards the development and use more formalised Quality Risk Management activities in the pharmaceutical GMP environment, present an ideal opportunity for the industry to begin identifying which systems are complex and tightly coupled. Then, Quality Risk Management efforts may be directed at the most highly complex and coupled systems

first. As discussed further in Chapter 7 (Section 7.2.8.2), this could be achieved via rigorous process mapping studies, which can visually indicate system complexities and couplings in an easy to understand manner. Such work may help to prioritise Quality Risk Management activities, and it may help ensure that risk control strategies are not invalidated by unforeseen system characteristics, complexities and couplings.

1.5.3.3 Risk Communication

ICH Q9 defines Risk Communication as "the sharing of information about risk and risk management between the decision makers and others (9)." It states that "communications might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc." and that "the output/result of the quality risk management process should be appropriately communicated and documented (9)."

ICH Q9 explains that the information being communicated "might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality (9)."

There are also other accepted definitions of Risk Communication. The Canadian Standards Association, whose Risk Management Standard of 2002 gives perhaps the highest level of attention to Risk Communication activities of any Risk Management standard available, defines Risk Communication as "any two-way communication between stakeholders about the existences, nature, severity, or acceptability of risks (81)."

The communication of risk and the outcomes of risk assessments is a key part of any Quality Risk Management activity, yet this is an area that is often not proceduralised adequately in existing Quality Risk Management methodologies and procedures. As discussed by Nivolianitou in 2002, regardless of how good the risk assessment activity may be, the inability of experts to communicate risks and the outcomes of risk assessments in an effective manner can have detrimental effects (69). These can include "conflicts and controversies surrounding risk and environmental impact", and Nivolianitou contends that "it is essential that technology experts understand the

complex psychological, social, cultural and political forces that dictate success and failure in risk assessment and risk management (69)."

Kaplan and Garrick (77) make an interesting point in relation to risk communication, and how it may serve to actually reduce risk. (This is useful when considering what risks may need to be communicated during Quality Risk Management exercises.) When discussing safeguards that may be used in order to reduce risk, Kaplan and Garrick promote the simple idea that risk awareness is an important safeguard in itself that may actually help to reduce risk. An example of this is making automobile drivers aware about "a hole in the road around the corner" to reduce the risk presented by the hole in the road (77) to those drivers. The idea that *making people aware of a risk can help reduce that risk* is a concept that may be used when defining risk communication activities during a risk management exercise, as any action that serves to help reduce risk should be considered in any risk management strategy (77).

1.5.3.3.1 Problems associated with Risk Communication activities

Risk Communication is perhaps the most important component of Quality Risk Management for which problems of risk perception play a vital role. In any Quality Risk Management process, it is important that the risks which are identified for the item under study are communicated to decision makers, stakeholders and other interested parties in a way that minimises problems of mis-perception. Thus, clear and formal guidelines should be documented within the Quality Risk Management process for how risk communications are to occur, and by whom.

Much research has been performed in some areas in relation to risk perception issues, and how different groups perceive risk has been shown to be important (87, 96-99). This is because, when there are differing views and opinions among stakeholders on the significance or importance of a particular risk, it can be difficult to reach agreement on the acceptability of that risk, or on the suitability of a coarse of action proposed to address the risk, if one is required. For example, one group might believe that strong risk mitigation measures are required to address a particular risk, while another group may believe that the risk at hand is not one which requires any mitigation at all. It is

important therefore to give consideration to issues relating to risk perception when determining risk communication activities during Quality Risk Management.

The literature shows that, to date, there has been little, if any, work done in GMP-related environments on how problems of risk perception may apply to GMP-related risks. It is likely, however, that risk perception is as relevant to GMP-related environments as it is to other industries, such as the insurance, nuclear and aerospace industries.

The pharmaceutical industry is one in which technology plays an important role, and in relation to technology, Nivolianitou (69) and others (98, 100) have written extensively about the need for the general public to be trained on how to perceive risk figures and to be able to compare voluntary and involuntary risks, in order to "rationalise the fear and aversion against modern technology (67)".

In his 1981 review of the application of Probabilistic Risk Assessment techniques to energy technologies, Rasmussen (82) discusses how "societal preferences" for different types of risks are important for decision makers to consider when making public policy decisions on the basis of the results of risk assessments. This is because, public official "decision makers must be responsive to public preferences (82)". ICH Q9 also acknowledges that risk perception is an important issue, stating: "each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm (9)".

The research that has been performed on the factors that influence risk perception is useful when incorporating Quality Risk Management activities into pharmaceutical GMP environments. For example, in relation to the insurance industry, Litai's work at the Massachusetts Institute of Technology in the late 1970s produced a listing of nine so-called quantifiable 'risk factors' which, when applied to different risks, were used to indicate how risks were perceived by the general public (96). A dichotomous scale was developed which accompanied each risk factor, allowing risks to be classified by selecting one of the two options from the scale for each risk factor. See Table 1.1 below for details. Litai (96), Starr (97) and others also developed weightings (or Risk

Conversion Factors) for each risk factor, in an attempt to reflect in numerical terms the relative importance to the public of the various risk characteristics. These Risk Conversion Factors were used to score different risks, and relative risk perception scores were thus determined.

Table 1.1: Latai's Risk Factors (1980):

Risk Factor	Dichotomous Scale	Risk Conversation Factor
Volition	Voluntary : Involuntary	100
Severity	Ordinary : Catastrophic	30
Origin	Natural : Man-made	20
Manifestation of Effects	Delayed : Immediate	30
Exposure Pattern	Continuous : Occasional	1
Controllability	Controllable : Uncontrollable	5-10
Familiarity	Common/Old Hazard : Dread/New Hazard	10
Benefit	Clear : Unclear	10
Necessity	Necessary : Luxury	1

Litai's work suggested that the public was willing to accept risks that could be considered voluntary - an example would be the risk from smoking cigarettes - up to 100 times the magnitude of risks that were considered to be involuntary (such as the risks posed by high voltage electricity lines located near one's home.) This was the case even when the risk associated with some voluntary activities was estimated to have been a lot larger than some often cited risks that are involuntarily assumed. For example, Keller performed an analysis of death rates in the US per annum for various 'risky' activities and situations, and classified these as either voluntary or involuntary (98). Keller found that the calculated risks associated with voluntary activities, such as motorcycling, receiving surgical anaesthesia and smoking, were found to be significantly higher than risks that were involuntarily assumed, such as rail travel accidents, being struck by lightening, and suffering from influenza (98).

It should be noted, however, that Litai's *Risk Conversion Factors* shown in Table 1.1 are not considered to be either absolute or an accurate model of risk perception for all applications. Litai's risk factors and their associated Risk Conversion Factors were

derived from an extensive analysis of the database of a major US life insurance company (96), and other researchers in this area have attributed sometimes quite different Risk Conversion Factors to the same risk factors. Starr (97), for example, assigned a Risk Conversion Factor of 1000 to the Voluntary:Involuntary Risk Factor, which was ten times higher than that assigned by Litai (96).

As discussed by Morgan in a widely quoted Scientific American paper from 1993 (87), a great deal of research has also been performed by experimental psychologists into how risks are perceived, and several research studies identified similar influencing factors to those identified by Litai. The work of Slovic and Fischhoff in the late 1970s, for example, indicated that such factors may be grouped into three main categories - the degree of 'dreadfulness' associated with the risk, the degree to which the risk was understood, and the number of people exposed to the risk in question (94). Slovic and his colleagues used these categories to define what was called a 'risk space', and when a hazard came within that space, it was argued that a person's perception of the risk associated with that hazard tended to be significantly affected. Such findings can be useful when determining how to communicate risks during or following Quality Risk Management exercises performed in a GMP environment. This is important because, as explained in more detail below, the factors which may relate to risk perception issues may influence how the outputs of Quality Risk Management exercises may be judged and accepted by decision makers and stakeholders following risk communication activities.

The findings from the above and other experimental psychology studies also demonstrate the important role that human heuristics (or unconscious rules of thumb) may play in the perception of risk.

Research by Kahneman at the University of California at Berekley has shown that the so-called heuristic of 'availability' appears to greatly influence how people make judgements about things which are uncertain, and this includes risks (92-93). This was shown to lead to systematic bias and other errors in judgement.

The heuristic of availability relates to the fact that people tend to judge the likelihood of an event in terms of how easily they can recall (or imagine) examples (92-93). Thus, a

person's ability to recall an event, (this could be, for example, a proposed failure mode identified during a GMP Quality Risk Management exercise) or to imagine a scenario happening, can strongly influence how that person makes a judgement about the likelihood of that event.

Kahneman's research found that people tend to underestimate the frequency of very common hazards, and overestimate the frequency of very rare hazards (89, 92). Again, from a Quality Risk Management perspective, this is important, because this heuristic may influence how the outputs of Quality Risk Management exercises may be judged and accepted by decision makers and stakeholders. For example, when this heuristic is operating, people on the receiving end of risk communications may not accept one or more of the findings of the Quality Risk Management team in relation to the acceptability of some risks. They may strongly disagree with an estimate of the probability of occurrence assigned to a particular failure mode or hazard that may lead to a particular risk, or they may disagree with the severity rating assigned by the team to the potential effects of that hazard.

Process experts are often employed when Quality Risk Management exercises are being performed. As discussed by Garfield in 1982, (99), the work of Fischhoff et al, (94), demonstrated that an expert's perception of risk can differ markedly from that of the general public. Fischhoff's work showed how lay people tend to regard as 'risky' any technology that is new, imposed on them, unfamiliar and beyond their control. Such findings are also important considerations when performing GMP-related Quality Risk Management exercises, given the different groups and stakeholders to whom risk information may be communicated, and the highly technical nature of GMP activities.

In his text titled 'Risk Assessment and Risk Management in the Pharmaceutical Industry', and recognising the work of Morgan (100) and others, Vesper presents a useful discussion on the elements of a good risk communication strategy (50). Some of these elements have been incorporated as guidance for the Quality Risk Management methodology developed by this author. These are presented in italics below, and briefly discussed thereafter:

- *Identify the stakeholders of the Risk Management exercise, and determine those stakeholders to whom risk communications should be made following the Risk Management exercise (50):*

This helps to determine the audiences for the risk communication activity, the actual content of the risk communication, and the technical level at which to pitch the risk communication message. With respect to the application of Quality Risk Management in GMP environments in relation to Qualification, Validation and Change Control activities, it is the author's opinion that not all stakeholders in the item under study may need to receive direct risk communications. For example, while patients are clear stakeholders of any process that produces, controls or regulates medicinal products, it may not be useful to communicate the outcomes from Quality Risk Management exercises that are focussed on Qualification, Validation and Change Control activities. Certain stakeholders will, however, likely be interested in the outcome of such Quality Risk Management exercises, such as GMP Inspectors and Assessors at a competent authority, senior management and other staff at the company concerned, or customers purchasing the pharmaceutical product or service.

It is important also to determine the needs of the particular audience to whom communications will be made with respect to a Quality Risk Management exercise, and to consider the level of information the audience may already have on the item under study. This allows the risk communication message to be tailored accordingly. GMP inspectors may be technically versed in the item under study, and may be highly interested in the detail of how the risks were arrived at, in the risk mitigation measures proposed, and in how compliance with the applicable GMPs was achieved. Senior management at a pharmaceutical company, on the other hand, (while they may also be concerned with those same things), may be less technically familiar with the details of the item under study, and may be more interested in the cost and resource implications of the recommendation arising from the Quality Risk Management exercise.

- *Ensure that the person or persons designated to communicate the outcomes of the Quality Risk Management exercise are credible, trustworthy, honest, and have the*

necessary level of expertise to field questions and explain the Risk Management process and its outcomes (50):

It is tempting to only appoint persons who are considered 'experts' in the item studied in the Quality Risk Management exercise to be the *risk communicators*. This may not always be beneficial however, and others may be better communicators for the audience at hand. Vesper points out that experts sometimes "use terminology that is technically correct but which overwhelms the lay stakeholder (50)." Even in GMP applications when the audience for the risk communication may comprise of technical people such as engineers, chemists and GMP inspectors, it is important to recognise that these people may not have the same degree of technical knowledge in the technology underpinning the item under study as the risk communicator may have.

- *Ensure that the content of the risk communication is balanced and open, and not manipulated by bias or ulterior motives (50):*

There will usually be some uncertainty associated with the outcomes of the Quality Risk Management exercise. It is thus important to openly communicate significant sources of uncertainty and any pertinent assumptions relating to the Quality Risk Management process and its outcomes. Vesper discusses how the "fair and balanced inclusion of other, conflicting, points of view" can "shape how recipients feel about the [Risk Management] process (50)." It is important also to truthfully report the findings of the exercise, without manipulation of the results or data to suit the desired outcome.

- *Before risk communications are carried out, study the risks generated by the Risk Management exercise to determine whether particular risks might be mis-perceived by the people to whom the risk communication is targeted (50):*

An example here might be the risks associated with glass or other particulates in injectable medicinal products. Such risks might fall into Fischhoff & Slovic's high "dreadfulness" group of risks discussed above (94). And in accordance with Litai's risk factors (96), this type of risk could also be characterised as an involuntary risk, with perceived catastrophic consequences. These are the types of risk that research has

shown to be subject to the problems of mis-perception, as discussed above. Thus, it would be important during any risk communication activity on such risks to clearly describe how the risk is controlled at a practical, detailed level, in clear and definite terms.

Research has shown that problems of mis-perception can be reduced during risk communication activities when stakeholders have had an opportunity to participate in the Risk Management process or in the item under study at an early time-point (89, 100-203). In GMP environments, this can be difficult to achieve in practice, because of the highly confidential and controlled nature of API and medicinal product manufacturing. However, there are opportunities in this area. For example, a company may proactively invite GMP Inspectors to review and discuss early parts of a Quality Risk Management exercise that is underway, such as the list of potential failure modes or negative events that were identified and which will be studied in detail during subsequent steps of the Quality Risk Management process. In this way, the Inspector will not be surprised when he/she reads of the failure modes and their associated risks when the final report on the Quality Risk Management exercise is being reviewed during inspection.

1.5.3.4 Risk Review

ICH Q9 states that the quality risk management process should "continue to be utilized for events that might impact the original quality risk management decision", whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall) (9).

In this regard, ICH Q9 recommends that "the output/results of the risk management process should be reviewed to take into account new knowledge and experience", and that a "mechanism to review or monitor events should be implemented (9)". Such new information may include process experience gained since the previous Quality Risk Management exercise was performed, as well as deviation records, quality defect reports, near-miss incidents, rejected batches, etc. Risk review activities also might include reconsideration of risk acceptance decisions. With respect to the required frequency of any such review, ICH Q9 states that this "should be based upon the level of risk (9)."

As an example to demonstrate the importance and usefulness of Periodic Review activities during Quality Risk Management work, it is useful to consider the experience of the US *Nuclear Regulatory Commission* (NRC) in this regard.

In the United States, the NRC is the legislative body which regulates and licenses the country's commercial nuclear power plants. The use of formal Risk Management methodologies at the NRC is well established in the literature (57-62, 82, 103), and these methodologies have been under continuous improvement since the 1970s, when the first major Risk Management exercise was carried out on two commercial nuclear power plants, in a study known as the Reactor Safety Study (103).

The Reactor Safety Study (discussed in detail in Chapter 7 of this thesis) was performed between 1972 and 1975 (103). It represented the first documented, formal and comprehensive application of Risk Management in the nuclear arena, utilising what are called Probabilistic Risk Assessment (PRA) techniques. (Note: PRA is also discussed in detail in Chapter 7.) The results of that study had significant implications for how the US nuclear power industry would be regulated in the decades that followed (e.g. see Ref. 58). During the 1980s, technology advancements allowed for the development of new computational models for severe nuclear accident processes, and at the NRC, this led to improved Probabilistic Risk Assessment methods of analysing the physical processes of severe nuclear plant accidents (60). By the late 1980s, approximately 40 US nuclear reactors had been assessed using PRA methodology, and a programme of re-assessments had begun (60).

The first major re-assessment exercise that was carried out was published in the NRC report known as NUREG 1150 (60, 62). This involved a formal review of the results of the 1972-1975 Reactor Safety Study, and the application of more up-to-date PRA methodologies to the same two commercial nuclear power plants as studied in the Reactor Safety Study, as well as three others (60). The PRA methodologies used in the NUREG 1150 study had advanced significantly since the 1972-1975 work. This was not just as a result of the evolution of more sophisticated computational techniques since the 1970s; there were also advances in other key areas. For example, the use of expert judgement had been a feature of the Reactor Safety Study, but in the NUREG

1150 re-assessment study, more formalised and documented procedures had been employed for the elucidation and documentation of expert judgements, particularly with respect to "obtaining probability distributions for uncertain parameters (60)."

The above 1989 review by the NRC exercise generated important results and insights into the factors which can lead to different results from Risk Management exercises performed on the same items under study (60). The NRC found very different results for the probabilities of core meltdown accidents for the two common nuclear power plants which had been assessed between the first PRA exercise in 1975, and the next exercise in 1989 (60). There were two main reasons attributed to these differences. Firstly, it was recognised that the PRAs which had been performed in both studies were "snapshots in time", taken about 15 years apart, and during this time, the nuclear power plants had "implemented hardware modifications and procedural improvements with the stated purpose of improving safety", thus driving core damage frequencies downwards (82). Secondly, it was recognised that significant advances had occurred in applying probabilistic analysis techniques in nuclear power plant applications since the Reactor Safety Study had been performed, and this "reduced or eliminated previous analytical conservatisms (82)". In addition, "computational techniques were now more sophisticated", and the level of detail in reactor modelling "had increased enormously (82)".

The new 1989 PRA studies had proven beneficial in other ways too. In those re-assessment studies, new types of failures were uncovered which had not been identified in the Reactor Safety Study (60). For example, the 15 years of experience between the two PRA studies had shown that failures could occur in the reactor coolant pump seals, and this had not been known at the time of the Reactor Safety Study in 1972-1975. In addition, intersystem dependencies had been uncovered in the 1989 review work which also had not been known at the time of the Reactor Safety Study. This review work generated important new results which presented a somewhat different picture relative to that obtained from the Reactor Safety Study for the estimated safety of nuclear energy compared with other energy sources, such as coal.

Other periodic review activities performed by the NRC in the US demonstrate the learnings that may be gained when new knowledge and more advanced methodologies

are applied to previous Risk Management exercises. Rasmussen, chairman of group which performed the pivotal Reactor Safety Study on two US nuclear power plants in the 1970s, demonstrated how Litai's Risk Conversion Factors (96), discussed above in relation to Risk Communication, could be applied to some of the nuclear power plant safety risks calculated in the original Reactor Safety Study (82). Rasmussen applied Litai's Risk Conversion Factors to some of the specific nuclear fatality risks which had been calculated in the Reactor Safety Study. From the calculations performed, it was concluded that "although nuclear power is still below the other curves [i.e. showing relative fatality estimates for different energy producing technologies], it no longer appears to be as insignificant a risk as was shown in the original WASH-1400 *[(7)]* comparison (82)." Rasmussen stated that these studies on risk perception "suggest some interesting ways to look at risk comparisons that give important insights as to why some technologies have serious problems of public perception (82)."

The above discussion illustrates the importance of effective Periodic Review activities during Risk Management and Quality Risk Management activities.

1.5.4 Quality Risk Management Methodologies (Tools)

As stated in the Introduction, there are numerous formal Quality Risk Management methodologies available. Some of these are inductive (or forward thinking), methodologies, which progress from cause to consequence. Examples include Event Tree Analysis (ETA) (50), Failure Modes and Effects Analysis (FMEA) (44, 46-47), Failure Modes, Effects and Criticality Analysis (FMECA) (47), Preliminary Hazard Analysis (PHA) (50), Hazard and Operability Studies (HAZOP) (63-64), and Hazard Analysis and Critical Control Points (HACCP) (48-49).

There are also deductive (or reverse thinking), methodologies available, which run from consequence to cause, and these include Fault Tree Analysis (45, 50), Common Cause Failure Analysis (CCF) (63), Ishikawa (Fishbone) analysis (84) (also known as Cause and Effect Diagrams), Master Logic Diagrams (56), among others.

There are some Quality Risk Management methodologies which can be considered to be a combination of two or more of the above. Examples include Human Factors

Engineering (104, 105) and Human Reliability Analysis techniques (106), which seek to model the role of human error prior to, during and following accidents, and Probabilistic Risk Assessment (PRA) (56, 57), which is a set of methodologies that is extensively used in the aeronautics and nuclear power generation industries, and is discussed in some detail in Chapter 7 of this thesis.

The above methodologies vary widely in the level of detail and rigor applied to the problem at hand, or to the area or process under study, and some are more quantitative than others. For example, Fault Tree Analysis (45) is generally used in a highly quantitative manner, especially when used as a component within a Probabilistic Risk Assessment-based approach (56). Ishikawa (Fishbone) analysis, on the other hand, is generally used in a more qualitative manner (84). FMEA-based applications can be described as ranging from qualitative to semi-quantitative (44, 46-47).

There are also many less formalised Quality Risk Management methodologies available, such as simple brainstorming and 'what-if' questioning techniques, and these can be used to identify and manage the risks associated with hazards. See Vesper (2006) for a comprehensive review of many formal and less formal Quality Risk Management methodologies for pharmaceutical applications (50).

While many of the above methodologies incorporate some of the items and components which make up the Quality Risk Management process as defined in ICH Q9, none of the above tools was designed to serve as a complete, documented and ready-to-use Quality Risk Management methodology, encompassing all of the elements of ICH Q9. This is because certain aspects of the four main components of Quality Risk Management (i.e. Risk Assessment, Risk Control, Risk Communication and Risk Review) were not addressed or incorporated in the design of those methodologies.

Fault Tree Analysis (45) and Event Tree Analysis (50), for example, are methodologies that were not designed to characterise or estimate the magnitude of the risks associated with faults or accident scenarios in the process or item under study. HACCP was not designed to specifically estimate the magnitudes of the different risks which may be associated with any one hazard (48-49), and FMEA applications generally do not

formally include Risk Communication or Periodic Review activities as part of the work items to be addressed when using these methodologies (44).

There are also many Quality Risk Management–related activities that are poorly developed (or not developed at all) within current methodologies. These include carrying out brainstorming activities, (e.g. for identifying and documenting potential failure modes & their causes), and dealing with the problems of subjectivity and uncertainty which can arise during Quality Risk Management exercises, as described in ICH Q9 (9).

In the author's experience as a GMP Inspector, and from a review of the literature as well as from discussions with other Inspector colleagues and industry representatives, the most widely used Quality Risk Management methodology in the pharmaceutical industry at this time is FMEA. Stamatis described FMEA as "a specific methodology to evaluate a system, design, process or service for possible ways in which failures (problems, errors, risks, concerns) can occur" and one which "provides a systematic method of examining all the ways in which a failure can occur" (44). Omdahl, in 1998, described FMEA as "an engineering technique, used to define, identify, and eliminate known and/or potential failures, problems, errors, and so on from the system, design, process and/or service before the reach the customer (107)."

FMEA is a formal, inductive and systematic Quality Risk Management methodology, normally executed using multi-disciplinary teams, on parts of a process or item under study (46). There are different types of FMEA which may be used. McDermott et al, 2006, define two broad types of FMEA – Product FMEA and Process FMEA (51). Stamatis, on the other hand, in his 2003 book titled 'Failure Mode and Effect Analysis: FMEA from Theory to Execution' describes four main types of FMEA, System, Design, Process and Service FMEA (44).

FMEA has been used as a formal Risk Management methodology within a number of industries for several decades, and its use is now highly advanced in some areas, such as in military and aerospace applications (51). In the automotive manufacturing sector, Stamatis outlines the extensive use made of FMEA by the three major US automobile manufacturers, Ford, Chrysler and General Motors (44). Stamatis discusses how each

company has its own FMEA-based standard, such as Ford's Q101 FMEA standard, and the General Motors 'Targets for Excellence' FMEA-based certification standard. Each of these three companies has also required, as far back as 1986, FMEA programmes to be in place at their suppliers (44).

In 1980, the US Department of Defence Military Standard titled 'Procedures for Performing a Failure Mode, Effects and Criticality Analysis (FMECA)' provided the first highly detailed description of the structure and nature of FMECA as a Risk Management methodology (47). This Standard also provided comprehensive guidance on how to actually carry out FMECA-based Risk Management exercises. FMEA, a somewhat simpler and less mathematical version of FMECA, was also described in some detail in this Standard. Since that time, there has been extensive coverage in the literature of FMEA and FMECA-based methodologies and their applications.

One of the main differences between FMEA and FMECA is the inclusion of what is known as a 'criticality factor' in FMECA (47). While Risk Priority Numbers (RPNs), which are the product of the severity, frequency of occurrence and detection-ratings assigned to a failure mode, are the main basis by which to prioritise failure modes for risk mitigation activities in FMEA, the calculated criticality associated with failure modes as a function of severity is the basis by which to prioritise failure modes for risk mitigation activities in FMECA. Failure mode criticality is calculated either as the product of the consequences of a failure mode and its frequency of occurrence (46), or, the product of the consequences of a failure mode and a value known as the criticality number for that failure mode. The latter parameter is termed *Cm* (46), and is dependent upon several variables, including the probability, β, of a failure effect occurring. In FMECA, a matrix is generated showing the distribution of the criticality values for failure modes as a function of their severity. In this way, priorities can be assigned to the corrective actions required to address each failure mode. See the aforementioned US Military Standard for a more complete description of how failure mode criticality is determined (47).

1.5.5 Risk Management Standards

A number of Risk Management standards have been developed in the last decade in order to formalise and standardise the application of Risk Management and its methodologies at national as well as international levels. Some of these standards are of a general nature, such as the Risk Management standard published by the Canadian Standards Association in 2002 (81), while others were tailored to a specific industry or field, such as the Risk Management standard for Medical Devices that was finalised by the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC) in December 2000 (108).

The earliest risk-related standard published was the Norsk standard titled 'Krav til riskoanalyser' published by the Norwegian standards organisation Norges Standardiseringsforbund in 1991 (109). While this standard focussed mainly on risk analysis activities and did not extend to wider Risk Management activities such as risk communication, it was a useful starting point. Other more comprehensive standards followed, the three most comprehensive (in this author's opinion) being the Risk Management Standard for Medical Devices published by ISO/IEC (108), the 2004 Australian and New Zealand Risk Management standard (80), and the Canadian Risk Management Standard of 2002 (81).

The publication in 2002 of ISO/IEC Guide 73:2002, titled 'Risk Management – Vocabulary - Guidelines for use in standards' (110) helped to standardise some of the terminology that is used today in Risk Management publications and standards. The National Standards Authority of Ireland (NSAI) described the ISO/IEC Guide 73:2002 as one that provides a "basic vocabulary of the definitions of risk management generic terms", aimed to "encourage a mutual and consistent understanding and a coherent approach to the description of activities relating to the management of risk (79)."

A number of the Risk Management standards published by national and international official accreditation bodies, such as the Canadian Standards Association (79), as well as by professional organisations, such as the Institute of Risk Management in the UK (111), were subject to a comprehensive review by Raz and Hillson in 2005 (76). This

review, which extended to nine published Risk Management standards, (all relatively recent, the oldest going back to 1997), presented a number of interesting findings, and many common features were found between all of the standards reviewed.

Raz and Hillson found that while there were substantial differences in the scope of the various standards reviewed, and also in the level of detail covered by each, all of the standards were relatively similar in the Risk Management process employed by each. Three main components were identified in the Risk Management process presented by each standard - risk identification, risk analysis and risk treatment/reduction. Other common components were identified also, such as planning for the Risk Management exercise, monitoring/controlling the risk management process, and the effectiveness of risk treatment actions (76).

In addition, Raz and Hillson found that:

- With respect to the risk identification step, a large number of different tools and techniques were prescribed by the various standards for identifying hazards and their related risks. Almost all such tools and techniques were descriptive and qualitative in nature, such as checklists, cause and effect diagrams, Hazard & Operability Studies (HAZOP), root cause analysis techniques, and scenario analysis. Only a few techniques (such as event tree analysis and quantitative fault tree analysis) were based on statistical or mathematical techniques.

- Within the risk analysis steps, which was a core activity of the Risk Management process employed by each standard, most of the standards differentiated in some way between risk estimation, (which involved an estimation of risk on the basis of the likelihood of occurrence of a hazard and the potential consequences of that hazard), and risk assessment, (which concerned the valuation of an estimated risk against a set of accepted criteria).

- Differences in terminology were observed in many areas, especially in relation to areas generally considered under the term risk analysis. For example, in some of the standards, risk analysis was called risk assessment, and in others, one was

considered a subset of the other. Generally however, terminology differences between the standards were not found to be significant.

- In relation to risk treatment, Raz and Hillson found significant differences in the level of detail and rigor given to this area between the various standards reviewed (76). For example, while the 2001 Japanese International Standard titled 'Guidelines for Development of Risk Management System', (112), devoted detailed sections to risk treatment activities such as the selection of risk treatment strategies, dealing with emergency risk situations, and resuming operational activities as a result of risk treatment actions, other standards, such as the 2004 Project Risk Analysis and Management (PRAM) Guide of the UK Association for Project Management (113), deal with such activities in much less detail.

One of the main differences between the nine standards reviewed by Raz and Hillson was the inclusion in some standards of important activities not considered to be central to Risk Management activities in some of the other standards. For example, activities such as risk communication and consultation with stakeholders, and the integration of the Risk Management process into the organisation performing the Risk Management exercises, were prominent in the 2004 Risk Management standard of Standards Australia and Standards New Zealand (80), and in the Canadian Risk Management Standard (81), but not so much in others.

Although Raz and Hillson (76) concluded that a "wide consensus" existed in relation to "the main steps and activities of a generic risk management process", and that there was "universal consensus" on what constituted "the central risk management process", in this author's opinion, these findings, coupled with the author's own experience in discussing Risk Management strategies with a wide range of pharmaceutical-related stakeholders, including GMP Inspectors and pharmaceutical companies, suggest that there is still probably not a general consensus on what activities actually constitute Risk Management.

This is probably set to change, however. In 2005, the International Organization for Standardization (ISO) began working on the development of a generic Risk Management standard to be known as 'ISO 25700 - Risk management — Guidelines on

Principles and Implementation of Risk Management' (79). This new Standard, which was still in draft form at the time of writing (December 2007) and which has since been renumbered to ISO 31000, is intended to have wide applicability across a range of industry and regulatory environments (79). At the time of writing, the Standard was at Committee Draft (CD) stage, meaning that a relatively advanced version of the document had been arrived at and was ready for deliberation by the ISO Committee for that Standard.

The National Standards Authority of Ireland (NSAI) has described this new ISO standard as "a generic standard intended to provide a common approach in support of standards dealing with specific risks and/or sectors and does not intend to replace those standards (79)." It has stated that "the standard gives generic guidelines for the principles and the adequate implementation of risk management" and that "it is not intended to be used for the purposes of certification (79)."

In setting out the need for this new ISO Risk Management standard, the NSAI explained on its website how there are "a number of risk-related standards published by ISO and other standards bodies, as well as many standards that refer to risk management, but there is no central ISO document that provides a consistent approach (79)." In the absence, however, of an explicit process for the management of risks, the NSAI stated that "these standards can cause confusion among users regarding practical interpretation and implementation (79)."

In conjunction with developing the above new ISO Risk Management Standard, the ISO Risk Management Working Group responsible for ISO 31000 is also working on updating the aforementioned ISO/IEC Guide 73 - Risk Management – Vocabulary (110), in order to reflect the terminology being used in ISO 31000. Chapter 8 of this thesis, titled Conclusions and Recommendations, provides a brief discussion of some of the features of the new ISO 31000 Risk Management Standard.

1.6 Research Aims and Objectives

1.6.1 Overall Goal of this Research Work

The overall goal of this research work was to develop a Quality Risk Management methodology that served as a practical solution for facilitating compliance with the risk-based Qualification, Validation & Change Control GMP requirements of the EU, and which was fully in line with the principles and guidance of ICH Q9.

1.6.2 Specific Research Objectives

Specific research objectives were defined for this work. These were as follows:

Research Objective No. 1:

To develop a Quality Risk Management methodology designed to facilitate compliance with the risk-based Qualification, Validation & Change Control GMP requirements of the EU. In this regard,

- The methodology should be in line with the principles and guidance of ICH Q9. Thus, the evaluation of risk by the methodology should ultimately link back to a potential harm to the patient, and the level of effort, formality and documentation provided by the Quality Risk Management process should be commensurate with the level of risk. Also, the methodology should serve as a readily usable, documented and complete Quality Risk Management solution, without requiring extensive modification before it may be used to address all of the elements of Quality Risk Management as defined in ICH Q9.

- The methodology should have wide applicability across a broad range of areas within the GMP-regulated environment as a solution for determining, on a risk basis, the scope and extent of validation and the likely impact of changes. The assessment of deviations, for example, is an area within the GMP-regulated environment to which the methodology should be applicable. This is because

qualification and/or validation work may be required following certain deviation incidents, in order to demonstrate the adequacy of corrective actions (such as process, equipment or procedural changes) that may be implemented to prevent a recurrence of the deviation, and it is important that such qualification and/or validation work relates to the risk(s) presented by the deviation.

- The methodology should offer a Quality Risk Management process that is value-adding, not only in facilitating compliance in the GMP-regulated environment with the risk-based qualification, validation and change control requirements of the EU GMP Guide, but also, in facilitating Quality Risk Management training and educational activities.

Research Objective No. 2:

To develop a practical and detailed training programme on the use of this methodology. In this regard:

- Comprehensive training materials should be developed for facilitating training activities on the methodology;

- A documented strategy should be developed for the provision of such training in a timely and resource-efficient manner.

Research Objective No. 3:

To compare the approach to Quality Risk Management as developed in this work, in terms of best practice, with the application of Risk Management in two industries that can be considered to be mature and advanced in their use and application of Risk Management. In this regard:

- The US Aeronautics Industry, as represented by the work of the National Aeronautics Space Administration (NASA), and the US Nuclear Power Generation industry, as represented by the work of the US Nuclear Regulatory Commission

(NRC), were selected for this benchmarking exercise. These industries were selected for three main reasons:

- Formal Risk Management methodologies have been used by these industries for a considerable time period, (more than thirty years in each case), and the literature shows that both NASA and the US Nuclear Regulatory Commission have gained considerable experience in their application over that time period;

- The use of formal Risk Management methodologies by the above two industries has been extensive, and there is substantial evidence in the literature of continuous improvement activity taking place in the application of such methodologies at both NASA and the US Nuclear Regulatory Commission;

- The development of formal Risk Management programmes and activities at NASA and at the US Nuclear Regulatory Commission has been extensively described in the literature, and the problems and difficulties encountered by those industries in assessing and managing risk have also been well documented. This publicly-available information allowed the above benchmarking exercise to be carried out effectively, as it facilitated a wide-ranging and detailed benchmarking exercise.

1.6.3 The Scope of this Work

The scope of this work extended to the application of Quality Risk Management within EU-regulated GMP pharmaceutical environments for Qualification, Validation and Change Control purposes. This includes both API and medicinal product manufacturing, control and distribution activities.

The scope of this work also extended to the application of Quality Risk Management across a wide range of activities in EU-regulated GMP pharmaceutical environments, such as:

- *GMP Processes*, such as Manufacturing processes, Cleaning processes, Packaging processes, together with their related items of equipment
- *GMP Systems*, such as HVAC systems, Building Management systems, Distribution & Recall systems, etc.
- *GMP Programmes*, such as Stability programmes, Complaint Investigation programmes, Pest Control programmes, Supplier Approval programmes, etc.

The scope of this work extended to the application of Quality Risk Management for retrospective use, not just prospective use. This was because, in the author's experience as a GMP Inspector, many companies were applying Quality Risk Management processes in a retrospective manner.

The scope of this work was confined to GMP-related pharmaceutical activities, and did not extend to non-GMP pharmaceutical activities such as Pharmacovigilance activities. This was because the aforementioned Annex 15 requirements do not apply to areas not regulated by GMP.

This work was not intended to address computerised system qualification and validation activities, because the application of Quality Risk Management in this area was already well established, and has been extensively covered in the literature and in official publications, (e.g. 55, 114-118). It also was not intended to address analytical method validation activities, because there was already legislation in place, e.g. via the European Pharmacopoeia (119), and official guidance ICH guidance, (120), relating to the scope and extent of validation required for analytical methods.

1.6.4 Research Methods

The research methods used in this research are set out in each of the individual chapters making up the research parts of this thesis. These are Chapters 2, 3, 4, 5 & 6.

In Chapters 2 through 4, the research methods that were used related to the development, testing and evaluation of the first three versions of this Quality Risk Management methodology.
In Chapter 5, the research methods that were used related to the identification of the sources of subjectivity and uncertainty during Quality Risk Management activities, and to the development of practical strategies for incorporation into the design of this methodology to address those sources of subjectivity and uncertainty.

In Chapter 6, the research methods that were used related to the development of the final version of this Quality Risk Management methodology, and to the development of a comprehensive training programme, together with documented training materials, for the methodology.

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Chapter 2

Design, Development, Testing & Evaluation of the initial version of the Quality Risk Management methodology

2.1 Introduction

The initial stages of this research involved the **design and development** of the first version of the Quality Risk Management methodology. This was a relatively basic version of the methodology, designed to primarily focus on the Risk Assessment and Risk Control elements of the Quality Risk Management process, which represented the back-bone of the methodology, around which all other elements would fit. The methods used in the above design and development work, and the results thereof, are presented in Sections 2.2.1 and 2.3.1, respectively, below.

A practical and GMP-related **Case Study** was then developed using this version of the methodology to demonstrate how the methodology worked in practice and to facilitate the preliminary testing that was to be performed on the methodology. Details of the development of this Case study, and the results thereof, are presented in Sections 2.2.2 and 2.3.2, respectively.

Preliminary testing was then carried out on the methodology, involving two key stakeholder groups – GMP Inspectors at the Irish Medicines Board, and the pharmaceutical manufacturing sector in Ireland. This preliminary testing work was designed to help gauge the level of regulatory and industry interest in the methodology, and the relevance of the methodology as a potential solution for addressing the risk-based Qualification, Validation and Change Control requirements of the EU GMP Guide. The methods used in the above preliminary testing work, and the results thereof, are presented in Sections 2.2.3 and 2.3.3, respectively.

Following the preliminary testing stage, more **detailed testing and evaluation activities** were initiated on this early version of the methodology. These activities were performed with post-graduate students from the Pharmaceutical Validation Masters Degree course at the Dublin Institute of Technology, Kevin Street, Dublin. These activities were designed to critically evaluate the methodology in a structured and formal manner. Further GMP-based case studies were used to challenge the methodology in a series of practical workshops, and a set of key research questions was developed in order to help structure the testing and evaluation activities. The methods

used in the above detailed testing and evaluation work, and the results thereof, are presented in Sections 2.2.4 and 2.3.4, respectively.

2.2 Research Methods

The following sections describe the research methods and activities that were employed in order to design, develop and test Version 1 of the new Quality Risk Management methodology.

2.2.1 Design and Development of Version 1 of the Quality Risk Management methodology

Three specific activities were carried out in order to design and develop Version 1 of the new Quality Risk Management methodology. These were the development of a set of Fundamental Principles upon which the Quality Risk Management methodology should be based, the development of a defined Quality Risk Management process for the methodology, and the development of a structured worksheet which users of the methodology would use to document the Quality Risk Management exercise.

2.2.1.1 Development of a set of Fundamental Principles for the methodology

A set of Fundamental Principles upon which the Quality Risk Management methodology should be based was developed. This was so that the methodology would serve as a practical solution for meeting the EU GMP risk-based Qualification, Validation and Change Control requirements.

These principles were also intended to provide the basis for the design and development of the Quality Risk Management process which the methodology would use.

2.2.1.2 Development of a basic Quality Risk Management Process

Based on the aforementioned underlying principles, and taking into account the practical requirements for the methodology as defined in Research Objective 1 (stated in

Chapter 1), a basic Quality Risk Management Process was developed which sets out the key steps to be carried out when using this methodology.

2.2.1.3 Design of a structured and practical Worksheet for the methodology

On the basis of the above Quality Risk Management process, a structured and practical Worksheet was designed as a template for applying the Quality Risk Management process to a manufacturing process or other GMP-related activity/item.

This worksheet was also designed to guide and instruct users of the methodology as they worked through the various steps of the Quality Risk Management process.

2.2.1.4 Assembly of Version 1 of this Quality Risk Management methodology

Following development of the above components (i.e. the Fundamental Principles underlying this approach, the Quality Risk Management Process for the methodology, and the Worksheet to be used by the methodology), the first version of this methodology was assembled.

An Introductory presentation on the methodology was also prepared, in order to describe this approach to Quality Risk Management, and to outline some of the main features of the methodology.

2.2.2 Development of a practical, GMP-related Case Study using Version 1 of the Methodology

A practical, GMP-related Case Study on the methodology was then developed, in order to demonstrate how the Quality Risk Management process and its accompanying worksheet worked at a practical level, and how the methodology served to facilitate risk-based Qualification and Validation activities for the item under study.

A pre-requisite for this case study was that it had to represent a real-life situation or specific problem that had been encountered in a medicinal product manufacturing plant.

The case study that was developed involved the application of the methodology to the manufacturing process of a paracetamol suspension-based medicinal product, for which problems had been identified during the final mixing and filling stages. The company on which the case study was based manufactured a range of medicinal products, including suspensions, and it was located in the EU. Several of the details presented in the case study, however, including details of the particular medicinal product involved, were changed when the case study was developed, in order not to divulge the identify of the company or the product concerned.

2.2.3 Preliminary testing of Version 1 of the Methodology

As mentioned in the Introduction, two key stakeholder groups were identified for presenting the methodology to as part of this preliminary testing work. These were a) GMP Inspectors at the Irish Medicines Board, and b), members of the GMP-regulated pharmaceutical manufacturing sector in Ireland.

2.2.3.1 Preliminary testing with GMP Inspectors at the Irish Medicines Board

During September to October 2004, the methodology was formally presented to six GMP inspectors and other technical staff at the IMB for their review and critical evaluation. This included the IMB Director of Inspections (an individual who had previously served as a Senior GMP Inspector at the IMB), three Senior GMP Inspectors, two GMP Inspectors, and two other Inspectorate technical staff members.

An introductory presentation was given, which described this approach to Quality Risk Management, and in conjunction with the worksheet associated with this methodology, the fundamental principles upon which this methodology was based were set out. The key features of the methodology, as well as the Quality Risk Management process used by the methodology, were also described. The structure and purpose of the worksheet were discussed, and the aforementioned paracetamol-related practical case study was presented to, and discussed with, the group, to demonstrate how the methodology worked at a practical level.

The purpose of this testing was to facilitate a critical examination of the methodology by GMP Inspectors, and to obtain feedback in relation to the following:

- Whether there was a high level of regulatory interest in the methodology as a potential solution for facilitating compliance with the risk-based Qualification, Validation and Change Control requirements of the EU GMP Guide;

- Whether there were any general faults or problems identified with any aspect of the methodology from a regulatory perspective;

- Whether, from the GMP Inspector's point of view, the methodology was relevant to the needs and concerns of the pharmaceutical manufacturing sector as a potential solution for facilitating compliance with the risk-based Qualification, Validation and Change Control requirements of the EU GMP Guide.

2.2.3.2 Preliminary testing with the Irish Pharmaceutical Manufacturing Industry

In October 2004, the methodology was formally presented to members of the Irish pharmaceutical manufacturing sector. This took place at an Irish Medicines Board Inspectorate Information Day for Industry, held on October 15th, 2004 in Dublin, Ireland. Of the 222 attendees, approximately 155 of these (or 70%) were from the pharmaceutical manufacturing sector, from a wide range of companies.

A presentation was given which described this approach to Quality Risk Management, and the worksheet associated with this methodology was also presented. Together, these items set out the fundamental principles upon which this methodology was based. The key features of the methodology, as well as the Quality Risk Management process used by the methodology, were also described. The structure and purpose of the worksheet were discussed, and the aforementioned paracetamol-related practical case study was presented, to demonstrate how the methodology worked at a practical level.

The purpose of the above was to gauge the level of industry interest in the methodology as a potential solution for facilitating compliance with the risk-based Qualification, Validation and Change Control requirements of the EU GMP Guide (6), and to obtain

feedback on the relevance of the methodology in this regard. This was important because, if there was little interest in the methodology from an industry perspective, or if the methodology was perceived by those in attendance as having little relevance to the needs of the Irish pharmaceutical manufacturing sector, the methodology would likely need to be significantly modified before proceeding to test the methodology any further.

The presentation of the methodology at the Inspectorate Information Day was for general feedback only; the intention was not to evaluate whether there were any faults or problems with the methodology from an industry perspective. This was because this Information Day was a large, public event, and it was not considered to be an appropriate venue in which to expect industry representatives to provide comments on potential faults or problems with the methodology. However, any feedback in this regard was noted.

2.2.4 Detailed testing of the methodology with members of the Irish pharmaceutical manufacturing industry in a structured, academic environment

Following the completion of the preliminary testing work, more detailed and rigorous testing work began. This testing phase involved presenting the methodology to staff members of several Irish pharmaceutical manufacturing companies, and running a series of practical workshops with that group, in order to critically examine how the methodology performed when applied to a number of different GMP areas and activities.

The workshops were run in an academic environment, as part of a pharmaceutical validation master's degree programme at the Dublin Institute of Technology, (Kevin Street), Dublin. This environment was selected because it provided a group of post-graduate students who were already working in the Irish pharmaceutical manufacturing sector, and who had an active interest in qualification and validation activities. It also provided an environment in which a critical, rigorous examination of the methodology could be encouraged.

2.2.4.1 Series of Practical, GMP-related Workshops

A series of practical workshops were run on the methodology with staff members of several Irish pharmaceutical manufacturing companies, each of whom was studying Pharmaceutical Validation Technology at post-graduate (Masters Degree level) at the Dublin Institute of Technology (Kevin Street), Dublin.

These workshops were designed to challenge the Quality Risk Management methodology in a structured, formal and systematic way, by applying it to a number of substantially different manufacturing activities relevant to the GMP environment.

The manufacturing activities studied during the workshops comprised of:

- A **tablet film coating process** used in the manufacture of an immediate release tablet product (Workshop 1);

- A **Change Control proposal** associated with the drying steps of an active pharmaceutical ingredient (Workshop 2).

- The **early stages of a fermentation process** used in the manufacture of a biotechnology-based medicinal product (Workshop 3);

During each workshop, no proprietary or confidential information relating to the manufacturing processes under study were divulged, presented or discussed. No company documentation was used during any of the workshops, and the details of each manufacturing process were modified and generalised by the workshop leaders so that no proprietary or confidential information was divulged.

In order to train the workshop participants on the methodology before starting the workshops, the methodology was formally presented to, and discussed in detail with, the MSc group. In this regard, a detailed presentation was given on the methodology, and as before, this described the principles upon which this methodology was based, the key features of the methodology, and the Quality Risk Management process used by the

methodology. The structure and purpose of the worksheet was also described and discussed in detail.

The aforementioned paracetamol-related practical case study was presented during this training exercise to demonstrate how the methodology worked in practice, but in contrast to the earlier, preliminary testing stages described above, during this testing stage, the case study was discussed in considerably more detail, and each entry on the worksheet was critically reviewed and discussed in detail with the class.

2.2.4.2 Key Research Questions to be addressed during the GMP-related Workshops

The purpose of the workshops was to test and critically evaluate all aspects of the methodology, so that any **potential faults** in the methodology could be identified and corrected. Thus, prior to the workshops, a series of **key research questions** was developed to help structure the testing and evaluation activities during the workshops. These key research questions are set out in Table 2.1 below.

The first three key research questions focussed on testing and critically evaluating the principles upon which the methodology was based, the step by step process used by the methodology, and the design and structure of the components making up the methodology. (The components making up the methodology included the worksheet and the introductory guidance presentation that had been developed on the methodology by the author up to that time.) These three key research questions were designed to help identify potential faults in the methodology.

The fourth key research question related to how the methodology might be applied to an item under study, in terms of whether it should be applied at a very low level in the Item under Study (i.e. by applying it to each step of the process or procedure under consideration), or whether it be applied at a higher level, taking a more holistic view of the Item under Study and any potential concerns relating to it.

The fifth key research question was used to determine any key features of the methodology that required special training materials to be developed.

Any faults, observations or opportunities for improvement identified during any one workshop were discussed among the workshop participants and the author. These were formally documented and reviewed before the next workshop began. In this regard, any required modifications to the methodology, or any additional elements that were required in the methodology, were tested and evaluated in a practical, structured setting.

Following completion of the third workshops, all of the learnings gained during all three workshops were compiled and evaluated. Several required modifications and design improvements were identified from this review, and these were incorporated formally into the methodology. This resulted in the development of Version 2.0 of the Quality Risk Management methodology, as discussed in Chapter 3 of this thesis.

Table 2.1: Key Research Questions used during the detailed testing of the methodology with members of the Irish pharmaceutical manufacturing industry in a structured, academic environment

No.	Research Question
1	Are there any faults with the **principles** upon which this Quality Risk Management methodology is based which impact the ability of this methodology to facilitate compliance with the EU GMP risk-based Qualification, Validation and Change Control requirements?
2	Are there any faults with the **Quality Risk Management process** used by this methodology, which prevents the methodology from being a solution for determining, on a risk basis, the scope and extent of validation, and the likely impact of changes?
3	Are there any faults with the **design and structure of the worksheet and other components** making up the Quality Risk Management methodology, which prevent this methodology from being a scientific, practical, systematic, flexible, and ready-made solution to facilitate compliance with the EU GMP risk-based Qualification, Validation and Change Control requirements?

4	At what **level** should the methodology be applied within the Item under Study? In this regard, should it be applied to each step of the process or procedure under consideration, or should it be used at a higher level, taking a more holistic view of the Item under Study and any potential concerns relating to it?
5	Apart from general training activities on the Quality Risk Management methodology, what features of the methodology require special attention and guidance when developing **training materials** for users of the methodology?

2.3 Results & Discussion

In this Section, the results from the various design, developmental and testing activities outlined in Section 2.2 are presented and discussed.

2.3.1 Results from the Design and Development of Version 1 of the Quality Risk Management methodology

The results from each of the design and developmental activities outlined in Section 2.2.1 above are presented below. There were three such activities, namely, the development of a set of Fundamental Principles underlying this Quality Risk Management methodology, the development of the basic Quality Risk Management process for the methodology, and the design of a detailed Worksheet for the methodology. The results for each of these activities are presented and discussed in turn.

2.3.1.1 The Fundamental Principles underlying this Quality Risk Management methodology

A set of twelve principles were defined which provided the basis for the design and development of the Quality Risk Management methodology under development here. These are presented in Table 2.2, below.

These principles were determined following a comprehensive and critical review of the literature and a variety of other information sources that were relevant to this research area.

- The Risk Management methodologies and approaches (as described and referenced in Chapter 1) that were currently available and documented in the literature were reviewed, as were their applications (e.g. 26-28, 44-53, 55-57, 73, 80, 81, 108, 111, 113, 115, 117, 118).

- The review extended to current and upcoming (including yet-to-be finalised) official EU GMP guidance and regulatory requirements, particularly in the areas of Quality Risk Management, risk-based qualification and validation, and change control (e.g. 6, 9).

- Areas only indirectly related to Risk Management activities, but important nonetheless, such as uncertainty analysis and experimental psychology, were also reviewed (e.g. 86, 88, 89, 87).

- The author's experiences of inspecting pharmaceutical company Quality Management Systems, including qualification and validation activities, change control programmes and Quality Risk Management methodologies, served also as valuable sources of information.

The above reviews helped to determine what was important when defining the principles upon which to develop a Quality Risk Management methodology aimed at facilitating risk-based qualification, validation and change control activities within GMP-regulated environments.

Table 2.2: The Fundamental Principles underlying this Quality Risk Management methodology

No.	Fundamental Principle
1	The scope and extent of qualification and validation, and the likely impact of changes, should be determined and managed on a risk basis.
2	Risk is the combination of the probability of occurrence of harm and the severity of that harm, and that harm is considered to be damage to health, including the damage which can occur from loss of product quality or availability.
3	As a minimum, Quality Risk Management comprises of the following four components as defined and described in ICH Q9: Risk Assessment, Risk Control, Risk Communication and Risk Review,
4	A consideration of "what might go wrong" is fundamental to the Quality Risk Management exercise.
5	There may be some risks which cannot be eliminated or reduced to an acceptable level with current or realistic controls or resources, but which may be controlled to an acceptable level with improved detection or other measures, as determined on a case-by-case basis.
6	Quality Risk Management is not an exact science and, while a scientific approach should form the basis of the Quality Risk Management process, there may be uncertainties associated with the outcome of the Quality Risk Management exercise.
7	Risk may be assessed qualitatively as well as quantitatively, and a good qualitative assessment of risk may be more valid than a poor quantitative assessment.
8	The main stakeholders associated with the application of Quality Risk Management within GMP and Regulatory Compliance environments are patients & users of medicines, including healthcare professionals, as well as industry and regulators, and, while the concerns of all involved stakeholders should be taken into account in any Quality Risk Management exercise, protection of the patient is of prime importance, and therefore, Quality Risk Management should ultimately link back to the protection of the patient.
9	In GMP environments, a high detectability of risk does not necessarily mean that the risk is eliminated or adequately controlled.
10	The implementation of Risk Control measures could, in itself, inadvertently introduce new risks which may need to be managed.

11	Performing Quality Risk Management exercises can be improved through the use of multi-disciplinary teams.
12	A formal Quality Risk Management process may not always be necessary or appropriate, and the level of effort, rigor, formality and documentation associated with the Quality Risk Management exercise should be commensurate with the complexity and/or the criticality of the issue to be addressed.

The above Fundamental Principles are largely self-explanatory, but some background and explanatory information relating to each is presented below.

Principle 1 was based primarily on Annex 15 (Qualification and Validation) to the EU GMP Guide (6). It implies that, before any validation master plans and qualification & validation protocols are finalised, risks associated with the items under study should be considered, resulting in the identification of risk-based critical parameters or other attributes requiring qualification or validation. This Principle also implied that, before Change Control proposals are approved within a company's Quality Management System, the potential risks presented by the proposed change should be identified and assessed, and a strategy should be determined for managing such risks.

Principles 2, 3 & 4 reflected the guidance presented in an early draft of ICH Q9 (9) and in other official; publications, such as the ISO/IEC Guide No. 73, titled '*Risk Management – Vocabulary - Guidelines for use in standards*' (110). The specific inclusion of the loss of product availability in the definition of harm was considered important, particularly for GMP applications of Quality Risk Management. This is because the loss of product availability may adversely impact not only business-related parameters, but also the health of patients and users of medicinal products, due to that lack of availability.

Principle 5 reflected the author's experience of applying Quality Risk Management principles and tools to GMP situations and problems – in that sometimes, the probability of occurrence of harm, or the severity of that harm, just could not be reduced to levels which rendered the risk acceptable with current or realistic resources. Importantly, this principle recognised that some risks can be controlled to an acceptable level by means of detection or other risk control measures.

Principles 6 & 7 formally recognised that risks can be difficult to quantify, and that there may be uncertainties in the outcomes of any Quality Risk Management exercise. As discussed in ICH Q9, for example, different stakeholders may perceive different potential harms, or place a different probability on each harm occurring, or assign different severities to each harm, and this can lead to uncertainties. This principle implied that the Quality Risk Management methodology should be able to address such difficulties and uncertainties. (The publications numbered 28, 29 & 87, detailed in the References section of this thesis, provide useful information in this regard.)

Principle 8 required that the Quality Risk Management methodology, when designed, should help to formally identify who the stakeholders are for the item under study. This would enable the concerns of those stakeholders to be taken into account, and for appropriate definitions of Severity to then be determined.

Principle 9 was far reaching, and it rendered this methodology different to many other Risk Management approaches with respect to how risk detection was dealt with. Here, users may not automatically conclude that a high detectability of a potential failure mode or its effects means that a risk can be considered acceptable or adequately controlled. For example, the ability to detect glass particles in filled and stoppered vials may sometimes be high, but this detection control does not mean that the vial filling and sealing process is under adequate GMP control, if the incidence of glass in vials is relatively high.

Principle 10, also based on ICH Q9, meant that the Quality Risk Management methodology must formally be able to identify and manage any new risks which may be introduced as part of Risk Control activities. New risks may be introduced, for example, when a new PAT-based sensor is installed in a drying vessel at a manufacturing plant, to monitor a parameter such as water content in a batch of granulate or other processing material. The material housing the sensor may be incompatible with the contents of the dryer, or it may not be adequately robust, giving rise to a risk of product contamination.

Principle 11 recognised the benefit of using teamwork and multi-disciplinary teams when performing Quality Risk Management exercises, and was certainly not a new concept. Well established Risk Management tools such as FMEA (44, 46-47) and HACCP (48-49), had required the use of multi-disciplinary teams for years. This

principle, however, in formally emphasising the use of multi-disciplinary teams at this fundamental level, indirectly indicated that the methodology would have to provide specific and practical guidance for dealing with the common problems that are known to arise when teams are convened to carry out specific work. Such problems can include disagreements and differences in opinion among members, and the lack of participation by some individuals.

Finally, **Principle 12**, again reflecting the guidance of ICH Q9, recognised that much of what we do within GMP environments is risk-based, even if we do not call it that. This is important because, often, there may be no need to use a formal Quality Risk Management methodology when existing procedures or less formal approaches may be entirely adequate. This principle, in a subtle way, also recognised the fact that failure modes[4] and other events can sometimes have multiple causes, with multiple associated risks, and that some of those risks may be less important that others from a risk mitigating perspective. This can result in formal Quality Risk Management activities becoming costly, time-consuming and quite labour-intensive. This Principle recognised that if formal and rigorous Quality Risk Management methodologies are to be used, their use should be targeted at the most complex and/or critical issues to be addressed.

2.3.1.2 The Quality Risk Management Process

Based on the above fundamental principles, and taking into account the requirements for the methodology as documented in Research Objective No. 1, (documented in Chapter 1, Section 1.6.2), a structured and systematic Quality Risk Management process was developed.

At a high level, this process can be described as one which is based on the rigorous and formal identification of the Qualification and Validation requirements for all of the GMP controls that may be identified as being important in the control or mitigation of risks associated with the Item under Study in the Quality Risk Management exercise.

[4] The term 'Failure Mode' was taken to be synonymous with the term 'Hazard' for the purposes of this Quality Risk Management process.

Thus, this Quality Risk Management process involves the identification of failure modes associated with the item under study, and the GMP controls that are important in light of those failure modes. The risk(s) associated with those failure modes are estimated, assessed and re-assessed, taking into account the role played by both currently in place GMP controls, and any new GMP controls required for risk control or mitigation. The risk assessment and re-assessment activities, described below, require a probability of occurrence factor to be assigned to the potential causes of each failure mode, and a severity factor to be assigned to the potential consequences of the failure mode. A detection factor is also assigned to the failure mode, to reflect the level of detectability of the failure mode, its causes, or its consequences, by means of detection-based GMP controls.

The various probability of occurrence, severity and detection levels that may be assigned to any one failure mode during this Quality Risk Management process were presented in an introductory presentation on the methodology that accompanied the worksheet used by the methodology.

At a more detailed level, the Quality Risk Management process comprised of five major stages, within which were a series of individual process steps. A schematic of this process is shown in Figure 2.1, below, and the five process stages are then described in more detail.

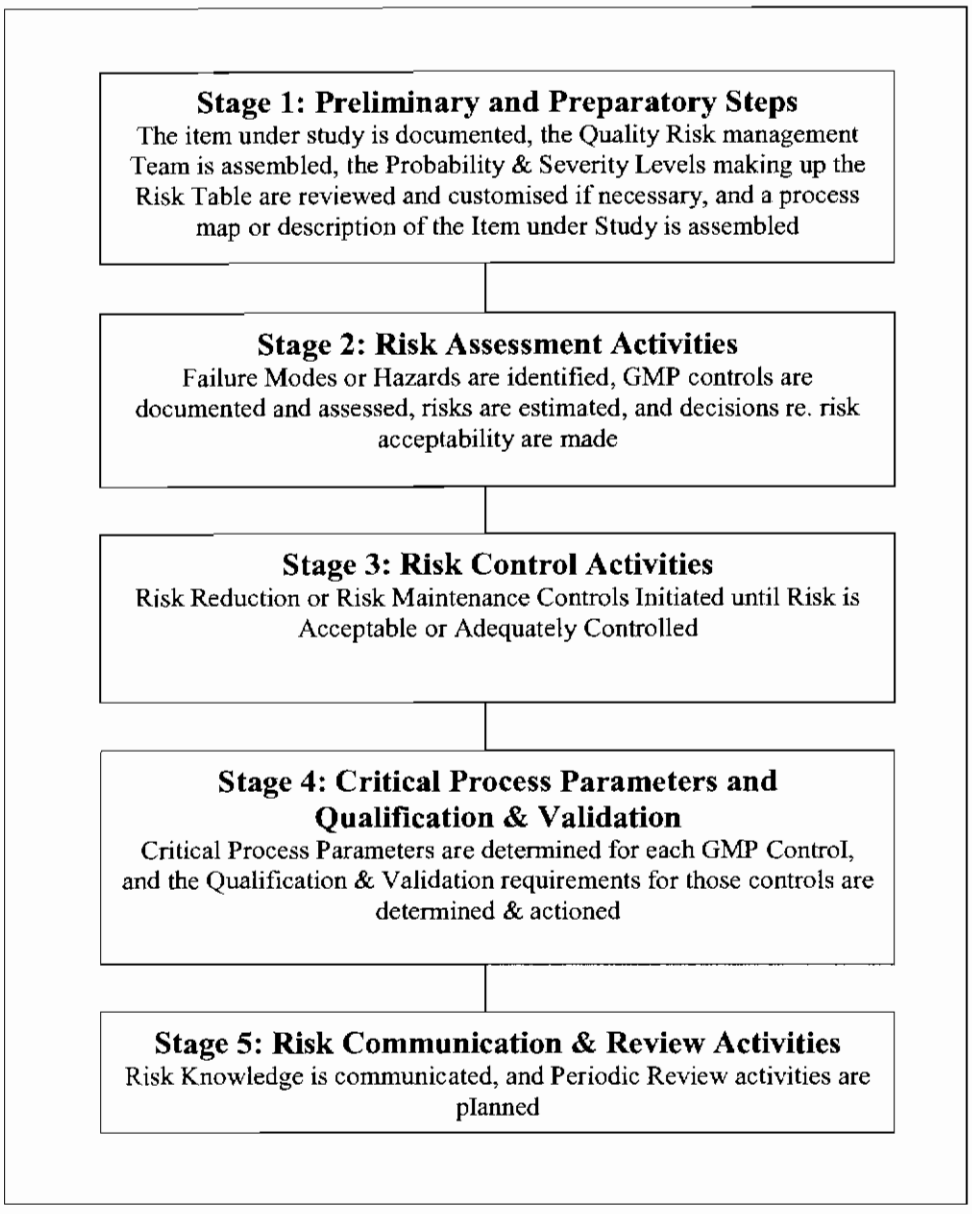

Figure 2.1: A Schematic of the Quality Risk Management process

The following is an outline of the steps involved in each of the five stages of this Quality Risk Management process:

Stage 1: Preliminary and Preparatory Steps for the Quality Risk Management Exercise

- The **Item under Study** (e.g. manufacturing process, or part thereof) to which the Quality Risk Management methodology will be applied is documented.

- A **Multi-Disciplinary Team** is assembled to perform the Quality Risk Management exercise, and a Team Leader is identified.
- The default **Probability of Occurrence levels,** as provided in an introductory presentation accompanying the methodology, are reviewed. Taking into account the type of data that are available on the item under study, any required modifications to these levels are discussed among the team, agreed and documented.
- The default **Severity levels,** as provided in the guidance documentation accompanying the methodology, are reviewed, and taking into account the stakeholders for the item under study, any required modifications to these levels are discussed among the team, agreed and documented.
- The **Risk Table**, as presented on the worksheet accompanying the methodology, which shows the risk acceptability criteria used by the methodology, is reviewed.
- The default **Detection levels** provided in the methodology are reviewed, and any required modifications to these levels are discussed among the team, agreed and documented.
- A **process map or description of the Item under Study** is generated or compiled; this is reviewed by the Quality Risk Management exercise.

Stage 2: Risk Assessment Activities

- Brainstorming and data review activities are carried out to **identify potential Failure Modes, their causes & potential consequences** for the Item under Study.
- Any **currently-in-place GMP controls** which may serve to limit the severity of the effects of each potential Failure Mode are identified, documented and critically evaluated, and a Severity rating is then assigned to the potential consequences of each potential Failure Mode, taking into account the controls identified above.
- Any **currently-in-place GMP controls** which may serve to limit the probability of occurrence of the cause of each potential Failure Mode are identified, documented and critically evaluated, and a Probability of Occurrence rating is then assigned to each cause of each potential Failure Mode, taking into account the controls identified above.
- Using the above **Severity and Probability of Occurrence ratings**, the **risk(s)** associated with the cause(s) of each potential Failure Mode are **estimated** using the Risk Table provided on the worksheet. In this way, the risk associated with each

cause of each potential failure mode is determined. The Risks will either be considered Intolerable, Unacceptable, or Acceptable.

- If a risk is deemed **Intolerable or Unacceptable**, the team must consider, document and critically evaluate what, if any, **detection controls** are currently in place that may serve to detect the potential failure mode, its cause, or its consequences, after the potential failure mode has occurred.
- A **detection rating** is assigned to the detection controls that are in place, but regardless of the detection rating assigned, the team is required to carefully evaluate whether the detection controls in question give **adequate assurance** that the risk in question is adequately controlled, and that no further risk mitigating controls are required.
- If the team considers that the detection controls in question do give adequate assurance that the risk is adequately controlled, and that no further risk mitigating controls are required, the team proceeds to the steps below, relating to **Critical Process Parameters and Qualification & Validation Requirements.**
- If the team considers that the detection controls in question do not give adequate assurance that the risk is adequately controlled, the team must proceed to the **Risk Control** stage of the process.

Stage 3: Risk Control Activities

- For each **Intolerable or Unacceptable risk**, the team works to identify any **risk control measures** that are required to reduce each risk in question to an acceptable level, or that may serve to control the risk to an acceptable degree. In this regard:
- **New controls** which may serve to limit the **severity** of the effects of this potential Failure Mode are identified, documented and critically evaluated, and a revised Severity rating is assigned to the potential Failure Mode, taking into account the new controls identified above.
- **New controls** which serve to reduce the **probability** of the cause of the potential Failure Mode occurring are documented and critically evaluated, and a revised Probability of Occurrence rating is then assigned to the cause of the potential Failure Mode, taking into account the controls identified above.
- The relevant steps described above in the Section titled "Risk Assessment Activities", are repeated, and **Risk Control activities continue** until either the risk

in question can be considered acceptable by the team, or, in the case of risks that are still considered Intolerable or Unacceptable, that the risk is considered to be adequately controlled on the basis of new detection controls.

Stage 4: Critical Process Parameters and Qualification & Validation Requirements

- Each control identified earlier in the process is now evaluated to determine any **critical process parameters** that are associated with it, and its associated limits or specifications.
- The **documentation** necessary to implement and monitor each control are determined.
- For each control, the Team determines whether any necessary **qualification or validation work** required has been carried out, and if not, the team determines and documents the qualification or validation work that is required.
- **Responsibilities** for completing each required validation or qualification action are assigned, and **target completion dates** for such work are agreed and documented.

Stage 5: Communication & Periodic Review activities

- The team reviews what, if any, **risk communication activities** are required arising from the Quality Risk Management exercise, and responsibilities are assigned in this regard
- The team decides when the Quality Risk Management exercise should be **reviewed**, and communicates this to the Validation Manager on site

The above process represented a systematic, rigorous and comprehensive approach to Quality Risk Management, encompassing all of the elements of Quality Risk Management as defined in ICH Q9. The process also offered considerable flexibility in enabling it to be used in a qualitative or quantitative manner, as the default qualitative nature of the process was designed to be easily modified to offer a quantitative approach, where required.

When designing the Probability of Occurrence, Severity and Detection tables for Risk Assessment and Risk Control stages of the process, several different scales, including

quantitative, semi- quantitative and qualitative were investigated. FMEA-type numerical scales (44, 51), in which the numbers 1 through 10 or 1 through 5 are used to rate Probability of Occurrence, Severity and Detection factors for potential failure modes were evaluated as possible options, but these were not used. This was in recognition of the fact that, because such scales are ordinal scales, their magnitude is not meaningful, and there is little to be gained by their use when qualitative phrases such as High, Medium, Low, Remote, Critical, Moderate, Minor, etc., offer more descriptive and easy to understand options. The research findings of Beth-Marom in 1982 (121) and Wallsten et al. in 1986 (122) were useful in this regard, as their research demonstrated that, when estimating the probability of an event and other uncertain parameters, people are usually more comfortable with verbal phrases than with numbers.

In addition, the use of qualitative word phrases over numerical labels was considered advantageous, in that it prevents the common problem of multiplying numerical values for Probability of Occurrence, Severity and Detection to generate numerical values for risks, or to generate Risk Priority Numbers (RPNs), when there is no mathematical basis for such multiplications, given the ordinal nature of those numerical scales (52, 123). This is still a common feature of some Quality Risk Management methodologies (26, 44, 51).

Thus, qualitative phrase-based levels (such as *Frequent, Probable, Occasional, Remote, Critical, Major, Minor*) were used instead of numerical-based levels (such as numbers *1, 2, 3, 4*) when designing the default levels for Probability of Occurrence and Severity that were used to construct the Risk Table used in this methodology. These Probability of Occurrence and Severity levels, as well as the Risk Table, are shown in Table 2.3 below.

Note that similar qualitative phrases for the detection levels used by the methodology in Stages 2 and 3 of the Quality Risk Management were also employed. These were the detection levels labelled *Low, Medium* and *High.*

Table 2.3: Risk Table for Version 2 of the Quality Risk Management methodology

Failure Mode	Minor Severity	Major Severity	Critical Severity
Frequent	Unacceptable	Intolerable	Intolerable
Probable	Unacceptable	Unacceptable	Intolerable
Occasional	Acceptable	Unacceptable	Unacceptable
Remote	Acceptable	Acceptable	Unacceptable

Legend:

- ***Intolerable** - The Risk is Intolerable. Eliminate the Hazard or build in systems/controls to ensure the effects of the hazard are not realised (e.g. via redundant systems).*
- ***Unacceptable** - The Risk is Unacceptable. The Risk must be Reduced or Controlled to an Acceptable Level.*
- ***Acceptable** - The Risk is Acceptable. No Risk Reduction or New Controls are required.*

As pointed out by Morgan et al in 1990, (89) however, such qualitative phrases are not without their own problems, as there can be "considerable variation" in the way different people interpret word-based phrases, and their interpretation can also be "content dependent."

A number of simple features were thus designed into the Risk Table in an effort to reduce such problems of subjective interpretations. For example, the Risk Table employs a relatively small number of Probability Levels (at four), and a relatively small number of Severity Levels (at three), compared with the approach used by some other Quality Risk Management methodologies, in which up to ten such levels are used in each case. In addition, simple definitions for the various levels in the Probability, Severity and Detection tables were included in the tables, to help users understand the meaning of each level. For example, the *Critical* level shown in the Severity Table was defined as a "Very Significant Non-Compliance with GMP or with the MA, involving possible Patient Injury".

2.3.1.3 The Worksheet for this Quality Risk Management methodology

A detailed, multi-section worksheet was designed for this methodology. This early version of the worksheet was structured around the Risk Assessment, Risk Control and Qualification & Validation parts of the Quality Risk Management process outlined

above. The worksheet also addressed the preliminary activities for the exercise, such as defining the item under study.

The purpose of the worksheet was to serve as an instructional template document for users of this methodology, in order to guide users through the above stages of the Quality Risk Management process, and to facilitate documentation of the exercise and its outcomes in a formal and structured manner. When completed, the worksheet served as a documented record of the main parts of the Quality Risk Management exercise, right from defining the item under study, right through to the planning of the qualification and validation activities required for any risk-based controls identified for that item under study.

The Communication and Periodic Review elements of the Quality Risk Management process were not addressed in this early version of the worksheet, as at the time of its development, additional research work was required in these areas, and it was decided that these areas would be addressed in a more developed version of the worksheet. The worksheet, as developed for Version 1 of this Quality Risk Management methodology, is shown in Figure 2.2, below.

2.3.1.4 Assembly of Version 1 of this Quality Risk Management methodology

Following development of the above components (i.e. the twelve principles underlying this approach, the five-stage Quality Risk Management process and the multi-page worksheet, the first version of this methodology was assembled.

An Introductory presentation on the methodology was also prepared, in order to describe this approach to Quality Risk Management, and to outline some of the main features of the methodology. In conjunction with the worksheet developed for the methodology, this presentation served to outline the fundamental principles underlying this Quality Risk Management methodology, and it described the way in which the methodology dealt with Severity, Probability & Detection factors. The Introductory presentation also described the Risk Table, and the way in which the Risk Table was structured to allow risks to be evaluated, and to allow for risk acceptance decisions to be made.

Taken together, the above four components made up the first version of this Quality Risk Management methodology. These components were:

- The Fundamental Principles underlying this Quality Risk Management methodology;
- The Worksheet used when executing Quality Risk Management exercises with this methodology;
- The five-stage Quality Risk Management process used by the methodology;
- An Introductory presentation on the methodology.

Figure 2.2: Scaled down version of the Worksheet (Version 1)

Cover Sheet

Risk Assessment & Risk Management Worksheet

Method: A Modified FMECA Method Combined with HACCP

Process Name:

Process Stage: **Process Step**:

Risk Table – Acceptance Criteria

Failure Mode	**Minor Severity**	**Major Severity**	**Critical Severity**
Frequent, >20%	Unacceptable	Intolerable	Intolerable
Probable, 5-20%	Unacceptable	Unacceptable	Intolerable
Occasional, 0.1 – 5%	Acceptable	Unacceptable	Unacceptable
Remote, <0.1%	Acceptable	Acceptable	Unacceptable

Intolerable
Eliminate the Hazard or build in systems/controls to ensure the effects of the hazard are not realised (e.g. via redundant systems)

Unacceptable
The Risk must be Reduced or Controlled to an acceptable level

Acceptable
No Risk Reduction or new Controls Required

Sheet 1

Sheet 1: Risk Assessment (Analysis + Evaluation)

Failure Mode			**Severity**		**Occurrence**		**Risk**
Potential **Failure Mode**	**Cause(s)** of this Failure Mode	Potential **Consequences & Effects**	* **Current controls** which limit the Severity of the effects of this Failure Mode	**S** **Severity** of the Effects of this Failure Mode should it occur	* **Current controls** which limit the probability of this Failure Mode occurring	**P** **Prob** of this Failure Mode occurring	**S x P** **Estimated Risk** (Risk Table) Acceptable, go to Sheet 4. Unacceptable, Intolerable, go to Sheet 2.

Sheet 2

Sheet 2 – Risk Control: Current Detection Controls

Current Detection Controls		Decision Point
* What **Current Controls** are in place which detect the Failure Mode or its effects after the Failure Mode has occurred	**D** **Rate these Detection Controls** (Low, Medium, High)	Do the current detection controls give **assurance** that the risk is adequately controlled & that no further controls are required? • If Yes, Go to Sheet 4 • If No, Go to Sheet 3

Sheet 3

Sheet 3 – New Risk Control Initiatives

New Severity Controls		New Occurrence Controls		New Risk	New Detection Controls		Decision Point
* What **new controls** will reduce the Severity of the effects of this Failure Mode, (e.g. redundant systems)	**New S** **Severity** of the Effects of this Failure Mode	* What **new controls** will reduce the probability of this Failure Mode occurring?	**New P** **Prob** of this Failure Mode occurring	**New Risk** Associated with this Failure Mode (Use Risk Table)	* What **new controls** will increase the detection of the Failure Mode or its effects after the Failure Mode has occurred?	**New D** New **Detection** Rating (Low, Medium, High)	**Do these measures now ensure** that the Risk is either reduced to an acceptable level or adequately controlled?

Sheet 4

Sheet 4 – Critical Process Parameters and Qualification & Validation Requirements

What are the **Critical Process Parameters** (CPPs) for the Controls in Columns * ?	What are the **Limits** associated with each CPP?	What are the **documentation requirements** to implement these CPPs?	Has each CPP been **qualified or validated** as appropriate? If no, what new qualifications of validations are required?	**Which Group is** resp. for Qual/Val? **Completion Date?**

2.3.2 Results of the Practical GMP-related Case Study developed using Version 1 of the methodology

A Case Study was developed using Version 1 of this Quality Risk Management methodology. This was in order to demonstrate how the methodology worked at a practical level, when applied to a GMP-regulated manufacturing process. (This Case Study is presented in Volume 2 of this thesis, as a component of the Training & User's Manual (discussed in Chapter 6) that has been developed for this methodology.) Some key aspects of the Case Study are presented below:

- The manufacturing process selected for this Case Study was that for a Paracetamol-based medicinal product. This was a suspension formulation, with a strength of 100mg/5ml, packaged in HDPE bottles with screw-top caps.

- The product was labelled as Paracetamol Suspension BP, for oral use, 100mg/5ml, and it was authorised in Ireland and elsewhere for paediatric use.

- The particular section of the manufacturing process to which the methodology was applied involved the final mixing and filling steps of the process. At this stage of the process, the final suspension was held and mixed in Vessel No. VS-04, prior to and during filling of the suspension into bottles. This section of the process was selected for study because recurring mixing-related problems had been observed in 2003 and 2004, and Vessel No. VS-04 had appeared to malfunction on a number of occasions when mixing & filling batches of this product.

- During processing of the batches in question, operators had recorded in batch records that the speed of the mixer had appeared variable and somewhat haphazard. A number of mixer stoppages had also been recorded, resulting in several deviation investigations during 2003 and 2004.

- This mixer was also used with several other suspension formulations, but the above problems had only been observed with this particular formulation, (No. 123), which was a relatively high viscosity suspension formulation.

- As part of an Annual Product Review that had been carried on this paracetamol suspension product, it had been decided to apply a Quality Risk Management methodology to help determine what, if any, new qualification and/or validation work was required for the mixing process or its related equipment. Thus, a retrospective application of this Quality Risk Management methodology to the above parts of this manufacturing process was performed. The Case Study related to that particular exercise.

During the case study, a number of different GMP controls were identified which related to the failure mode that had been documented for the mixing problems. (The failure mode was: "Mixer Malfunctions during Mixing of Bulk Suspension Prior to Filling.")

The controls in place that were relevant to this Failure Mode were documented and critically evaluated, and the risk associated with this Failure Mode was assessed as being Unacceptable. Following consideration of the detection-related controls which were in place, it was determined that new risk control measures were required. This led to new risk mitigating controls being identified, and several critical process parameters associated with those controls were documented.

This resulted in new equipment qualification work being required, which had not been identified prior to the completion of this exercise.

2.3.3 Results of the Preliminary Testing of Version 1 of the Methodology

The results from the preliminary testing of the methodology are presented below. Two key stakeholder groups were involved in this testing phase – GMP Inspectors at the Irish Medicines Board, and members of the Irish pharmaceutical manufacturing sector.

2.3.3.1 Results of the Preliminary Testing performed with IMB GMP Inspectors

During and following the presentation of the methodology and its associated Case Study to the GMP Inspectors and other staff of the IMB 's Inspectorate Department, a critical

examination of the methodology was performed. Certain aspects of the methodology were discussed in detail, particularly the way in which the methodology dealt with detection issues, with GMP controls, and with general qualification and validation activities.

From the feedback received by the author, it was evident that there was a high level of interest among the Inspectors and other Inspectorate staff in the methodology, as a relevant and practical solution for facilitating compliance with the risk-based Qualification, Validation and Change Control requirements of the EU GMP Guide. This was demonstrated not only by the verbal positive comments made to the author following the workshop, but also by the decision of the IMB Director of Inspections that the author should formally present the methodology and its accompanying Case Study on behalf of the IMB to the Irish pharmaceutical manufacturing sector. This would take place at the aforementioned 2004 IMB Inspectorate Information Day. The purpose of this presentation would be to publicly present the methodology and its associated Case Study as an example of how Quality Risk Management may be used within GMP regulated environments to facilitate compliance with the EU GMP requirements in relation to risk-based validation and change control, as set out in Annex 15 (6).

Notwithstanding the above, a fault was identified in the design of the Quality Risk Management process used by the methodology. During detailed evaluation of the methodology and the Case Study by a Senior GMP Inspector at the IMB, it was noted that no information had been documented in the Case Study on the qualification and validation status of the Item under Study *at the time* of the Quality Risk Management exercise. (The item under study in this exercise was the aforementioned paracetamol suspension manufacturing process.)

The Inspector felt that this gave the impression that there had been no qualification or validation work carried out on the manufacturing process. The Inspector explained that this would be an unreasonable approach to take, given that this was a retrospective application of the Quality Risk Management methodology to an already operational (and GMP-inspected) manufacturing process.

The author explained that the methodology did actually require an overview of the qualification and validation status of the item under study to be carried out prior to the application of the Quality Risk Management methodology to the item under study. This was demonstrated by some of the entries made on the worksheet in the case study, such as the following statements:

- "Initial PQ did confirm mixer achieved 80 +/- 5 RPM target at mixer set point, and process was validated at that time."

- "This viscosity still at upper PQ limit for mixer...."

- "Even though this in-process test is supported by process validation data, in the event of a mixer failure, one in-process sample does not provide adequate assurance of detection."

- "This in-process sample is supported by process validation homogeneity data."

However, it was recognised that the Quality Risk Management process used by the methodology did not explicitly require the qualification and validation status of the item under study to be documented. The author stated that this would be addressed via modification of the Quality Risk Management process.

No faults or problems were identified with the principles underlying this methodology or its key features. These were set out in the Introductory Presentation given by the author on the methodology in conjunction with presentation of the worksheet used by the methodology. In addition, no faults were identified with any aspect of the worksheet.

One Senior Inspector commented that the Introductory Presentation on the methodology was too long, and that some of the slides stating the references to risk in the EU GMP Guide should be moved into an Appendix at the end of the presentation. The introductory presentation was thus modified in this regard.

From the above feedback, and notwithstanding the two faults that were identified with the methodology, it was concluded that:

- There was a generally high level of regulatory interest at the Irish Medicines Board in the methodology as a potential solution for facilitating compliance with the risk-based Qualification, Validation and Change Control requirements of the EU GMP Guide.

- From a GMP Inspectors' perspective, the methodology was relevant to the needs and concerns of the pharmaceutical manufacturing sector as a potential solution for facilitating compliance with the risk-based Qualification, Validation and Change Control requirements of the EU GMP Guide.

2.3.3.2 Results of the Preliminary Testing performed with Industry

As outlined above, in October 2004 the methodology was formally presented to members of the Irish pharmaceutical manufacturing sector. This took place at the Irish Medicines Board's Inspectorate Information Day for Industry, on October 15th, of that year.

As there was limited time in which to present the methodology at this event, and given the general and public nature of the Information Day, this testing phase was limited to simply gauging the level of industry interest in the methodology, and the relevance of the methodology as a potential solution for facilitating compliance with the risk-based Qualification, Validation and Change Control requirements of the EU GMP Guide. (As documented earlier in this chapter, the Information Day was not used to evaluate whether there were any general faults or problems with any aspect of the methodology from an industry perspective.)

The Information Day was attended by 222 delegates, which included over 150 pharmaceutical manufacturing industry representatives from over 70 Irish and UK companies. The feedback received following the Information Day presentation was very positive, and the large number of verbal communications made to the author indicated that there was a high level of industry interest in the methodology. In this regard, senior staff members from four different pharmaceutical companies expressed

an interest in using the methodology within their own companies, and they requested an opportunity to learn more about the methodology.

One pharmaceutical company representative suggested that a detailed and practical workshop be run on the methodology in the near future, to facilitate the general development of Quality Risk Management in the pharmaceutical industry, in line with the aforementioned Annex 15 requirements.

With regard to the relevance of this methodology to the pharmaceutical manufacturing sector, the written feedback received by the Irish Medicines Board from attendees of the Information Day event demonstrated that the author's presentation on this methodology was considered to be highly relevant by that sector. In this regard, 94% of participants who responded to IMB's feedback questionnaire in relation to the Information Day assigned a positive score to the relevance of the presentation - 41% scored it as 'Good', and 53% scored it as 'Excellent' (124).

From the above feedback, it was concluded that:

- There was a generally high level of industry interest in the methodology as a potential solution for facilitating compliance with the risk-based Qualification, Validation and Change Control requirements of the EU GMP Guide.

- The methodology was relevant to the needs of the Irish pharmaceutical manufacturing sector in achieving compliance with the aforementioned risk-based requirements of Annex 15 to the EU GMP Guide.

2.3.4 Results from the Detailed Testing of the Methodology performed with members of the Irish Pharmaceutical Manufacturing Sector

The results for each of the five key research questions documented above are presented in this section, below.

First however, a brief overview of each of the three workshops run on the methodology is presented.

2.3.4.1 Overview of Workshop No. 1 - Application of the Methodology to a Tablet Film Coating Process

The purpose of this workshop was to apply the Quality Risk Management methodology retrospectively to a tablet film coating manufacturing process.

The following is an overview of how the workshop was run:

- A total of 14 people participated in the workshop; two of whom facilitated and led the exercise, and the remaining 12 acted as team participants.

- At the start of the workshop, a general overview of tablet coating operations was presented by the team leaders. While this included a general overview of film, sugar and press coating techniques, the team leaders focussed on film coating processes, as this was the process of concern here.

- The particular film-coating process of interest here was then presented, and the equipment used in the process was described.

- An outline of the common problems which were known to occur during film coating operations (e.g. twinning), were presented, and examples were given of solutions to some common coating problems.

- A process map for the film-coating process in question was presented to the class.

- Three groups of four participants were formed to apply the Quality Risk Management methodology to the film-coating process of concern. Each group was assigned a different part of the process.

2.3.4.2 Overview of Workshop No. 2 – Application of the Methodology to a Change Control in an API Manufacturing Process

The purpose of this workshop was to apply the Quality Risk Management methodology prospectively to a proposed Change Control at an API manufacturing facility. The Change Control involved a proposal to switch from using a cone dryer (based on centrifugation) to dry batches of the API in question, to a new Filter Dryer.

The following is an overview of how the workshop was run:

- A total of 12 people participated in this workshop; two of whom acted as team leaders and facilitators of the exercise.

- In response to learnings gained from Workshop 1, (discussed below), at the start of this workshop a more detailed description of the item under study was presented. This was made up of several specific elements, including:

  - An overview of the current API manufacturing process and the proposed changed process, with particular attention given to the isolation & drying steps in each;
  - A list of main equipment used in each process, as well as any facility ancillary equipment (such as a distributed control system) used;
  - A list of the current in-process tests and their limits for the new dryer process;
  - A list of the current finished API tests and their specifications;
  - A flow chart showing a high level outline of the current process;
  - A flow chart showing a high level outline of the to be changed process.

- The Workshop leaders presented a detailed batch manufacturing record for the *to-be-changed* API process, starting at the crystallisation stage of the process and ending in the packaging operations for the dried API.

- A more detailed overview of the Quality Risk Management process was presented to the team by the team leaders, and an outline was given as to how the workshop

would be run. (Again, this was the result of learnings gained from Workshop No. 1.)

- In response to certain difficulties encountered during Workshop No. 1 in relation to the way the methodology dealt with GMP controls, the author presented a detailed overview to the entire group on how the methodology dealt with GMP controls. This overview described and explained how the methodology required individual controls to be evaluated to determine whether they related to Severity, Probability of Occurrence, or Detection. A set of detailed examples and case studies was also presented in this regard.

- Prior to this workshop, it was decided that, instead of splitting the class into a number of smaller groups, each working on one part of the process under consideration, the full class would work together on the exercise at hand. This plan was used during this workshop.

- Also, instead of giving each participant a copy of the worksheet used by the methodology, as occurred during Workshop No. 1, for completion by each participant, during Workshop No. 2, the worksheet was reproduced in large size on a whiteboard, and the exercise involved the completion of this one worksheet by the team as one group.

2.3.4.3 Overview of Workshop No. 3 – Application of the Methodology to a Biotechnology-based Fermentation Process

The purpose of this workshop was to apply the Quality Risk Management solution retrospectively to the early scale-up steps in a fermentation process used in the manufacture of a biotechnology-based antibiotic medicinal product.

The following is an overview of how the workshop was run:

- A total of 13 people participated in this workshop; three of whom acted as team leaders and facilitators of the exercise.

- As in Workshop No. 2, at the start of this workshop, a detailed description of the item under study was presented. This was made up of a detailed overview of a general biotechnology-based fermentation process, in which a fermentation media is inoculated with genetically-modified CHO cells, allowing an antibody to be secreted during several fermentation scale-up steps. Harvesting, followed by large scale chromatography purification and concentration steps are carried out, and the resulting purified solution is filled. The main controls in the process were reviewed, and key viral inactivation steps were also discussed.

- As an aid to the team, the workshop leaders presented several examples of potential failure modes in the scale-up steps. One potential failure mode (the non-aseptic transfer of the fermentation slurry when transferring it from a small laboratory vessel to a larger bioreactor vessel) was selected. This failure mode was run through the Quality Risk Management methodology from start to end, in order to demonstrate how the methodology works in practice.

- As in Workshop No. 2, the Workshop leaders gave an overview of how the workshop would be run, stating that the exercise would be confined to the two early scale-up steps of interest.

- In response to learnings gained from Workshop No. 2, (as discussed below), a very simple Fault Tree Analysis approach was used to help identify potential Failure Mode in the item under study. Each of the two groups were given acetates of the blank Worksheet on which to record their findings from the exercise, and at the end of the exercise, the acetates were shown to the full class, and discussed.

- The workshop was led by three facilitators. The remaining ten team participants were divided into two groups, with each group assigned one part of the manufacturing process for evaluation using the Quality Risk Management methodology. One group applied the methodology to scale-up step 1, and the other to scale-up step 2.

2.3.4.4 Results for Key Research Question No. 1

Key Question 1 was as follows:

- *Are there any faults with the fundamental principles[5] upon which this Quality Risk Management solution is based which impact on the ability of the solution to facilitate compliance with the EU GMP risk-based Qualification, Validation and Change Control requirements?*

Eleven of the twelve principles were readily accepted by the group during the three practical workshops, and no faults were identified with any of them. Principle No. 9, however, which provided the basis for how this Quality Risk Management methodology dealt with detection issues, was not initially understood by the group, and the author was asked to explain this principle in more detail.

This principle states that in GMP environments, a high detectability of risk does not necessarily mean that the risk is eliminated or adequately controlled. The group required clarification of what this principle meant before they could accept it, as there was insufficient explanation given in the methodology on this principle. Also, one workshop participant asked why the methodology did not contain a GAMP 4-like detection feature (55), in which a risk-versus-detection matrix is used to show which risks are acceptable on the basis of detection ratings.

In order to better explain the above principle and the reasons for it, the author presented a brief GMP-related case study in which detection-type controls were important. (As this is the second Case Study presented in this thesis, it is numbered Case Study 2.)

[5] Note: at the time of Workshops 1 through 3, the fundamental principles were represented by points made in various parts of the documentation making up this methodology. (This included the Introductory Presentation and the Worksheet used by the methodology.) While the fundamental principles were not documented at that time as one comprehensive list, as shown in Section 2.3.1.1, above, the author explained each of these principles when presenting the methodology to the workshop participants.

2.3.4.4.1 Case Study 2 - Failure to record room differential pressures during aseptic processing

This case study involved the failure to record room differential pressures during the manufacture of a sterile medicinal product via aseptic processing. This case study related to a situation in which, when room differential pressure data were being reviewed by QA staff during batch review work prior to QP certification of a batch, it was noted that the record of the pressure differentials between the Class A/B room and the adjacent changing room was missing for one particular day.

(In aseptic processing, room pressure differentials of 10-15 Pascals are normally required between classified areas (6). These should be cascading outwards and downwards, from higher pressure to lower pressure. This pressure cascade is especially important when product and sterilised product contact components are exposed in a room or area.)

The case study described the procedures in place at the facility for recording and monitoring room pressure differentials. Operators in the aseptic suite were required to regularly record room differential pressures from Magnahelic gauges at the exit points in the rooms. (Ref: EU GMP Guide, Annex 1, Article 31.) These differential pressures were to be recorded not on the batch record, but on internal form F015. This was governed by an SOP, a copy of which was in the room. No second check of pressure differential data was being performed at the time of its recording. Form F015 was to be completed daily, and it was required to be attached to the batch record at the end of operations for each day of processing.

The Failure Mode in question was that an operator simply forgot to record pressure differentials during processing operations of a batch in the Grade A/B room. There had been several previous similar incidents in the past, albeit with different operators. One cause of the Failure Mode was that the operator failed to retrieve Form F015 and use it to record the room pressure differentials on the day in question. (It was noted that there was no instruction on the Batch Record to complete Form F015.) One of the potential consequences of this Failure Mode were that there was now no way to obtain direct verification that the required room pressure differentials had been met during the

processing of the batch on the day in question. From a sterility assurance perspective, documented evidence was not available to show that all of the required environmental conditions had been met during the aseptic processing of the batch in question, and no building management system was in place at the facility as a back-up system for such data.

In this case study, a large number of risk mitigating controls were documented that were relevant to the above Failure Mode. Each control was classified as to whether it related to the probability of occurrence of the Failure Mode, the severity of its effects, or its detectability. With respect to detection, the main control in this regard was that QA/QP personnel were highly likely to detect the missing pressure differential data during their review of the batch documentation. While this detection control had been assigned a high detection rating, the case study demonstrated how such a control did not serve to adequately control the risk presented by the Failure Mode from a GMP perspective. The batch had already been manufactured, filled and packaged by the time the Failure Mode was detected, and it was evident that a reliance on such a detection control, even though it had been assigned a high detection rating, was not an acceptable approach.

This Case Study demonstrated how sometimes a high detection rating for a Failure Mode does not necessarily address or control the risk associated with that Failure Mode. The author explained that this was the basis behind Principle No. 9, and it was why this methodology did not contain a risk versus detection matrix as in the aforementioned GAMP 4 methodology (55).

Following the presentation of this Case Study, the group then indicated that they now better understood Principle 9, and were satisfied that this Principle was appropriate and necessary.

2.3.4.5 Results for Key Research Question No. 2

Key Question 2 was as follows:

- *Are there any faults with the Quality Risk Management Process used by this methodology, which might prevent the methodology from being a solution for*

determining, on a risk basis, the scope and extent of validation, and the likely impact of changes?

During this series of workshops, two faults were identified with the Quality Risk Management process used by Version 1 of this methodology.

Fault No. 1 - Documenting Pertinent Assumptions:

The first fault was that the process did not require users to document or acknowledge any pertinent assumptions that may be relevant to the exercise at hand. This included, for example, assumptions in relation to the qualification status of the equipment used in manufacturing process under study, or in level of training given to staff members at the time of the exercise. During Workshop No. 1, a general assumption had been made that all of the required processing equipment would already have been qualified. It was observed, however, that this was too broad a statement, and many questions arose during the exercise about whether specific features and components of the tablet coating equipment had been adequately qualified. It was observed that clear and detailed documentation was not available to the groups during the exercise on the extent of qualification work that had been carried out.

It was also unclear during Workshop No. 1 whether the Quality Risk Management exercise was being performed on a new coating process, not yet validated, or on an existing and previously validated coating process, and no assumptions in this regard had been documented.

In Workshop No. 2 & No. 3, the greater attention had been given to documenting all pertinent assumptions that were relevant to the exercises at hand, and this included assumptions in relation to equipment and facility qualification, process validation and training. For example, during Workshop No. 2, the qualification work that would be carried out on the newly installed Filter Dryer was documented as a pertinent assumption as part of the Change Control proposal. This qualification work included the production and drying of a full scale (50kg) placebo batch of product prior to a Performance Qualification/Process Validation exercise that would also be performed using the new dryer.

Thus, the Quality Risk Management process was modified to require users to acknowledge and document in sufficient detail all pertinent assumptions that may be relevant to the exercise at hand. This approach proved to be beneficial, and it was observed that it facilitated the execution and completion of the Quality Risk Management exercises in a more timely and efficient manner than in Workshop No. 1.

Fault No. 2 - The Quality Risk Management process:

The second fault identified with the Quality Risk Management process used by Version 1 of this methodology related to how the process dealt with the nature and purpose of the Quality Risk Management exercise at hand.

During Workshop 1, difficulties arose approximately halfway through the exercise when it became apparent that the nature of the exercise, especially from a validation and qualification perspective, was unclear. Because the Quality Risk Management process did not formally require users to document whether the exercise at hand was a retrospective or prospective exercise, or whether it related to a Change Control proposal (also prospective in nature), the groups performing the exercise were unclear on what the nature of the exercise actually was. This was important because it hindered understanding the exact purpose and expected outcomes of the exercise. (This exercise was actually retrospective in nature, being applied to an existing tablet coating process.) As a result, during Workshop 1, it was not clear what the exact purpose of the exercise was, and the Quality Risk Management process did not formally require users to document this at the outset.

Thus, there was doubt during Workshop No. 1 as to whether the participants were expected to generate a full Process Validation protocol for the tablet coating process in question, or to critically evaluate the qualification and validation work carried out to date on this process and its equipment. It was not clear that, for this retrospective application of this methodology to the tablet coating process, the purpose of the exercise was to help determine retrospectively the Qualification & Validation status of the item under study, and the Qualification & Validation requirements for the item under study.

As a result of these learnings, the Quality Risk Management process was modified to require that the nature and purpose of the exercise to be explicitly documented and explained at the outset of each exercise. During Workshop No. 2 & No. 3, the exact nature and purpose of each Quality Risk Management exercise were clearly documented by the team leaders, and then discussed with the other team participants. During Workshop No. 3, for example, the team leaders documented and explained how this was a retrospective application of the Quality Risk Management methodology to two scale-up steps in a fermentation process – a process that had already been process validated. The purpose of the exercise was to use the methodology to help identify any additional risk-based Qualification & Validation requirements for each of the two steps of the process.

This modification to the Quality Risk Management process was observed to greatly facilitate the exercises at hand, and no questions were raised during the exercises on the nature or purpose of those Quality Risk Management exercises.

2.3.4.6 Results for Key Research Question No. 3

Key Question 3 was as follows:

- *Are there any faults with the design and structure of the worksheet and other components making up the Quality Risk Management methodology, which might prevent this methodology from being a documented, scientific, practical, systematic, transparent, flexible, and ready-made solution to facilitate compliance with the EU GMP risk-based Qualification, Validation and Change Control requirements?*

Several faults were identified with the design and structure of the Quality Risk Management methodology (Version 1). These are discussed below.

Fault No. 3 - Design of the Worksheet:

With respect to the worksheet, the design of the worksheet was found to be deficient in several ways. For example, it was noted during the workshops that the worksheet did not adequately address how the item under study (and its boundaries) should be

documented for the exercise at hand. In Workshop 1, neither the item under study nor its boundaries were clearly or adequately defined, and as a result, it was unclear whether the storage of uncoated tablets was part of the process to which the Quality Risk Management exercise applied or not.

A relatively brief overview of the tablet coating process, (called a process map), had been given by the team leaders at the start of Workshop No. 1. As the exercise progressed, however, this was found to have been too high level and not sufficiently detailed, and a generally poor understanding of the item under study was observed. This resulted in uncertainties in whether the exercise addressed the important risks or not.

During Workshops 2 and 3, the team leaders presented much more detailed descriptions of the items under study, and this proved beneficial. At the start of Workshop 2, for example, a completed Change Control form for the proposed dryer change was presented. The workshop leaders then presented a detailed overview (by means of a presentation) of the manufacturing process in question, paying particular attention to the isolation & drying steps of the current API process and those of the changed process. During this presentation, a list of the process equipment and a schematic diagram of the new filter dryer were also presented, and any ancillary facility equipment (e.g. a Distributed Control System) related to the process were documented. The known critical process controls for the current process were listed, and current in-process and finished product tests (as well as their specifications/limits) were documented. An overview diagram of the process outline (in flow chart form) was also presented, and this corresponded to the key steps in the Batch Production Record.

Having run through each step of the process with the team, and after presenting the above components, the workshop leaders questioned the group on the key steps and features of the process before starting the exercise, to establish that there was sufficient understanding of the item under study before formally starting the exercise. The above was observed to be effective at familiarising the team members with the item under study. Similar findings were made during Workshop 3.

Despite the above learnings gains from Workshop 1, there were still difficulties experienced during Workshops 2 & 3 in identifying and documenting the boundaries of the items under study for the purposes of the Quality Risk Management exercise. In Workshop 2, for example, it was stated that the boundary for the exercise started at where the new drying process differed from the current drying process; this was at Step No. 2.2 in the new process, (all earlier steps, including Step 2.1) were unchanged. However, the boundary had been documented as starting from step 2.1, not Step 2.2.

In Workshop 3, the boundary for the item under study had been determined by choosing a part of the process for study, defined by a start step and an end step. A detailed description of the item under study was then prepared, and this related only to the steps in the process captured by the boundary for the item under study. As the workshop progressed, however, it became evident that two key steps in the process – those being the preparation of liquid media and the preparation of liquid buffer – had inadvertently been excluded from the detailed description of the item under study.
This was realised when reviewing the in-process control tests which are carried out within the steps of the process included within the boundary for the item under study.

This omission hindered the Quality Risk Management exercise, as data and documentation had not been gathered on these steps for use during the exercise. One of the potential failure modes identified during the workshop related to the preparation of liquid media and buffer, and this potential failure mode was considered to be important, and required formal consideration.

The reason for the omission of these key steps was that these steps normally occur earlier in the manufacturing process then the thawing of frozen GM CHO cells, and the thawing step had been defined as the starting point when setting the boundary for the item under study.

The above learnings demonstrated the *importance of defining an appropriate boundary for the item under study*, as the boundary can influence the description of the item under study which is developed for the Quality Risk Management exercise at hand, and it can determine what data and documentation are collected as an aid to the exercise.

Problems were observed when the boundary of the item under study was finalised before a detailed description on the item under study had been drawn up.
The above workshops demonstrated that the boundary and description of the item under study are inter-related, with one depending on the other, and that it is beneficial to develop both elements at the same time.

In response to the above learnings, the following guidance was developed in relation to developing a boundary for the item under study and when compiling the required detailed description on the item under study.

- At the outset, a draft boundary should be defined for the item under study. This boundary may encompass the activities between two or more steps in a process, or it may be a collection of equipment or other process components, or a procedure or set of procedures.
- Next, a detailed description on the item under study should be assembled for the item under study, which defines the item under study in sufficient detail. This may include, for example, the following components:
  - An overview of the technology behind the Item under Study (e.g. a presentation on Tablet Coating, or Fermentation).
  - A copy of the actual (detailed) batch production record or SOP relating to the Item under Study, if one exists. For example, if the exercise relates to supplier approval activities, an SOP may be in place which describes the procedure for evaluating potential new suppliers. In some cases, however, it may be more useful to use an annotated description of the Item under Study – this is especially true with complex and multi-step processes or Items under Study. This might be a flow chart or a high level diagram describing the Item under Study.
- A list of the equipment relating to the Item under Study.
- A list of ancillary equipment and facilities (e.g. DCS) related to the Item under Study.
- Copies of any SOPs or other documents which are required to operate or run or comply with the Item under Study, such as SOPs for taking IPC samples from reactors, etc.

- A list of the Critical Process Controls for the Item under Study, as well as all in-process and finished product tests, and their specifications/limits.
- Copies of any validation reports (and their protocols) which relate to the item under study, where practical.
- Copies of any qualification reports (and their protocols) which relate to the item under study.
- If the Item under Study is a Change Control, both the current process/Item under Study and the to-be-changed process/Item under Study should be described in outline or flow chart format.
- When compiled, both the boundary and the detailed description of the item under study should be reviewed in order to determine if there are any aspects to, or steps in, the Item Under Study which are intended to be evaluated in this Quality Risk Management exercise, but which are not included within the boundary which has been defined for the Item Under Study.
- Note: The in-process control tests which are carried out within the draft boundary can be a useful source of information on key steps which may be carried out earlier than the starting point of the boundary of the Item Under Study.
- When this has been completed, the boundary of the Item Under Study should be finalised.

Fault No. 4 - Inadequate Guidance Documentation in the area of Failure Modes and related Brainstorming activities:

During the above series of practical workshops, a fault in the design of the documentation provided with the methodology was identified. It was observed that there was a lack of clear and definitive guidance provided in the documentation in relation to the procedures for identifying and documenting potential Failure Modes, and for performing brainstorming activities in relation to potential failure modes.

This hindered the application of this methodology in a number of ways. Specifically, there was a definite lack of rigor observed in Workshops 1 & 2 when failure modes were being identified and documented, and there was clear confusion observed between what was a potential Failure Mode, a cause and an effect. This subsequently led to problems in identifying risk-mitigating controls for the potential Failure Mode, because

the causes of such had not been well described. This also resulted in Failure Mode causes and associated controls not being correctly described or classified. In addition, the brainstorming activities carried out during those workshops were observed to be relatively unstructured and prone to issues of uncertainty and subjectivity. These issues are described in greater detail in a peer-reviewed research paper published by the author in the Journal of Validation Technology in February 2007 (125).

In response to the above observations and difficulties, a number of detailed, practical strategies for identifying and documenting potential Failure Modes, and for carrying out brainstorming activities in relation to potential failure modes, were developed and incorporated into the documentation provided with this methodology. Some of these elements and practical strategies are described in the aforementioned Journal of Validation Technology paper, and all are described in the Training & User's Manual that was developed to facilitate training and use of the methodology. See also Chapters 5 & 6 for more detailed discussions of the research findings in this regard.

Fault No. 5 - Inadequate Guidance Documentation in the area of GMP Controls:

During Workshops No. 1 and No. 2, a fault was identified in the design of Version 1 of the documentation provided with the methodology in relation to the handling of GMP controls. It was observed that methodology did not provide a clear, documented means of evaluating and classifying GMP controls relating to potential failure modes.

The worksheet did make provision for documenting the various types of controls pertinent to each failure mode, but it was unclear how the controls should be evaluated and classified in terms of their risk mitigating role.

In addition, participating team members did not appear to understand the meaning and role of the Severity-related controls identified during the workshop, and confusion was observed between what was a severity-related control and what was an occurrence and detection-related control. Confusion was also observed in what was meant by Severity controls generally, and what was a redundant control.

It was noted that the methodology did not contain any component that adequately explained or defined the different categories of GMP controls pertinent to the use of this Quality Risk Management methodology.

In response to the above observations, specific and documented guidance was developed for users of this methodology on how controls may be classified as either severity-related, probability of occurrence-related, or detection-related. In addition, guidance was developed on the specific meaning and role of Severity controls in this methodology, and on what is meant by the Severity element of risk.

In this regard, a guidance document titled "Understanding Severity Controls and the differences between Severity, Probability and Detection Controls" was developed. In addition, three GMP-related, practical scenarios were documented to demonstrate how various types of GMP controls, which were considered important in the scenario in question, should be classified when using this methodology. These scenarios were:

- *Scenario No. 1*: A failure with respect to environmental monitoring during the aseptic processing of a batch;
- *Scenario No. 2*: A failure in a pressure chart recorder used during operation of an autoclave;
- *Scenario No. 3*: A failure in the processing of an API batch relating to an incorrect pH measurement.

During Workshop 3, it was observed that the above guidance documentation enabled users to better understand the way in which the Quality Risk Management methodology dealt with GMP controls, and how such controls were to be evaluated and classified prior to the assigning of the severity, probability of occurrence and detection ratings to the failure mode in question.

Fault No. 6 - Design of the Risk Table:

During the detailed evaluation of Version 1 of the methodology, it was evident that the design of the Risk Table provided with the methodology had to be modified. The

required change related to how potential failure modes, which had been assigned a remote probability of occurrence and a critical severity rating, were assessed using the Risk Table.

The Risk Table used by Version 1 of the methodology required such risks to be considered *unacceptable*. However, when the design of the Risk Table was challenged using practical case studies and real-life GMP scenarios, particularly involving aseptic processing-related examples, it was found that the above classification of such risks as being unacceptable could not be supported given the current EU (and US) GMP provisions. Specifically, it was found that when potential failure modes were identified for which it was not considered possible to reduce the severity rating below that of *critical*, the current version of the Risk Table classified the risks associated with those failure modes as either *unacceptable* or *intolerable*, but never *acceptable*. This was irrespective of what rating had been assigned to the probability of occurrence of the causes of the potential failure mode. This was even the case when the probability of occurrence had been rated as *remote*, meaning that the cause of the potential failure mode was considered very unlikely to occur, and could not be reduced further.

Such situations, however, do occur during some GMP activities, such as in aseptic processing, and the current EU GMP guidelines explicitly allow for this, and indicate that this is an acceptable situation. Consider, for example, the requirements in relation to media fills at an aseptic processing facility. The current EU GMP Guide, in paragraph 43 of Annex 1, allows for a microbial contamination rate of less than 0.1% with a 95% confidence limit to be observed during media fill simulations when validating a filling process (6). This loss of sterility might have been the result of a failure mode relating to poor operator aseptic technique during the vial filling process, caused by perhaps an inappropriate hand movement by an operator working at the filling line. The probability of occurrence of this event might reasonably be considered to be *Remote*, (i.e. very unlikely to occur), but it is not zero, given the media fill result.

With regard to the potential effects of such a potential failure mode, it is reasonable to classify these as being *Critical*, in recognition of the harm the administration of a non-sterile solution to a sick patient might render. In addition, the nature of these effects is such that it is unlikely the Severity rating assigned to the potential failure mode can be

reduced. Using the first version of the Risk Table, the above *Remote* Probability of Occurrence rating and the *Critical* Severity rating translated into a risk that could never be considered as acceptable, yet the current EU GMP Guide considers such situations to be acceptable (6). Taking such learnings into account, the Risk Table was modified accordingly. The modified version is shown in Table 2.4 below.

Table 2.4: Modified Risk Table for Version 2 of the Quality Risk Management methodology

Failure Mode	Minor Severity	Moderate Severity	Critical Severity
Likely	Unacceptable	Intolerable	Intolerable
Occasional	Acceptable	Unacceptable	Intolerable
Unlikely	Acceptable	Acceptable	Unacceptable
Remote	Acceptable	Acceptable	Acceptable*

* Acceptable only with formal justification

***Legend**:*

- ***Intolerable** - The Risk is Intolerable. Eliminate the Failure Mode or build in systems/controls to ensure the effects of the Failure Mode are not realised (e.g. via redundant systems).*
- ***Unacceptable** - The Risk is Unacceptable. The Risk for this Failure Mode must be Reduced or Controlled to an Acceptable Level.*
- ***Acceptable** - The Risk is Acceptable. No Risk Reduction or New Controls are required.*

The revised table shows that such risks can be considered acceptable when there is adequate justification provided to support the risk acceptability decision. Part of such a justification would be to demonstrate that reasonable controls are in place (or will be put in place) which serve to reduce or limit the severity of the effects of the failure mode, even when that severity is still classified as Critical.

When a risk that is characterised on the basis of a *Critical* Severity rating and a *Remote* Probability of Occurrence rating is being assessed by the Quality Risk management team, before any such risk is deemed to be acceptable, the team is required to evaluate whether all that can be done has been done to reduce or limit the effects of the failure mode in question. This was the basis for the aforementioned revision to the Risk Table.

Fault No. 7 - Terminology used in this Methodology:

With respect to the terminology used by this Quality Risk Management methodology, certain terms used in Version 1 of the methodology were observed to be problematic for users of the methodology during the above practical workshops.

The terms 'Severity Control' and 'Probability Control' were used in Version 1 of the methodology to denote GMP controls that could serve to reduce the consequences of the effects of a failure mode, or its probability of occurrence. During the third workshop, following discussion with the workshop participants, it was decided that it would be better to use the term 'Preventative Control' instead of the term probability control, as it was more intuitively easy to understand and associate with the concept of failure mode probability of occurrence.

The 'Severity Control' terminology was used in the worksheet and documentation, and during the above workshops, it also was found to be difficult for users to intuitively understand. This term was ultimately replaced with the wording 'Controls in place which reduce or eliminate the effects of the failure mode, after the failure mode has occurred.' While this new wording is obviously much lengthier, and is somewhat more cumbersome than the term severity control, it is more descriptive in nature and is simpler to understand.

The 'Critical Process Parameter' terminology used in the worksheet was found to be problematic in some circumstances during Workshop No. 3. This issue is described in the peer-reviewed research paper published by the author in the Journal of GXP Compliance in July 2006, titled 'A Risk Management solution designed to facilitate risk-based Qualification, Validation & Change Control activities within GMP and Regulatory Compliance Environments in the EU - Part II – Tool Scope, Structure, Limitations, Principle Findings & Novel Elements (12).' Following detailed discussion with the workshop participants, the design of the worksheet was modified to address the difficulties identified with the critical process parameter terminology used in Sheet 4 of the worksheet. The worksheet was modified to allow the team to document 'Acceptance Criteria or Required Outcomes' for controls that did not have any clear critical process parameters associated with them.

While it took considerable time to develop the above strategies and documentation elements, a number of the strategies in question were incorporated into the methodology used during Workshop No. 3. It was observed that the identification and documentation of potential Failure Modes during this workshop was significantly improved.

Other Findings in relation to Research Question 3:

- **Methodology Usability Issues:**

With respect to the components supplied with the methodology to facilitate the efficient use of the methodology, during the course of the three workshops, different approaches were tested for using the methodology and completing the associated worksheet. This helped to determine the optimum method of applying the methodology in practice. While no faults were identified in this area, it was observed that the use of white boards and flip charts was beneficial during the brainstorming sessions in which potential failure modes were identified, and when their Severity, Probability and Detection ratings were being debated and assigned. During Workshop No. 1, these items had not been provided, and the exercise proved inefficient and disjointed, with little teamwork being observed. (Only a blank copy of the worksheet was made available to the three groups to work with during this Workshop.)

In Workshop No. 2, two large whiteboards and several different coloured markers had been made available to the group. The team leaders used these items to document the outcomes of the brainstorming exercise. In addition, the Workshop leaders had reproduced the exact content and structure of the worksheet on one of the whiteboards, and the group worked together to complete the worksheet. This approach proved beneficial and efficient, and a high level of teamwork was observed. It was noted, however, that the whiteboard entries were sometimes small and difficult to read.

During Workshop No. 3, a different approach was used. The two groups performing the exercise were supplied with acetates containing a blank version of the worksheet. As the groups worked through the exercise, they were requested to complete the worksheet with markers. At the end of the exercise, and using an overhead projector, each group presented the findings and outcomes of the exercise to the whole class towards using the

acetates now containing the completed worksheet. This approach was observed to also work well, and the use of acetates was found to be an efficient way of completing the worksheet and communicating the outcomes of the exercise.

Some participants of the exercise reported, however, that they found the acetate version of the worksheet to be more difficult to follow and less easy to use than the paper version of the worksheet. It was noted that the acetates containing the blank version of the worksheet did not have all of the explanatory text under the various worksheet headings that had been included in the original worksheet. Upon discussion, it was agreed that this was the cause of the above difficulties.

The Workshops showed that the worksheet did not have to be used in its original paper format, but whatever format was used to reproduce the worksheet, it was found that it was important to have all of the explanatory text under each heading included.

2.3.4.7 Results for Key Research Question No. 4

Key Question 4 was as follows:

- *At what level should the methodology be applied within the Item under Study? Should it be applied to each step of the process or procedure under consideration, or should it be used at a much higher level, taking a more holistic view of the Item under Study and potential concerns relating to it?*

During the three Workshops, the levels at which the Quality Risk Management methodology was applied to the item under study were investigated.

In Workshop No. 1, the methodology was applied to each individual step of the tablet film coating manufacturing process of concern. The three groups performing the exercise were asked to formally consider each individual step of the batch production record and identify what could potentially go wrong in that step. This was found to be an extremely laborious, time consuming and tedious exercise. A large number of potential Failure Modes were attempted to be processed in this workshop, and this did

not prove possible in the three hours allocated to the workshop, despite having three groups working on different parts of the manufacturing process.

The above approach represented the application of this methodology at a low, detailed level within the item under study. While this resulted in the generation of a large number of potential failure modes, in some cases, during the brainstorming activities, the individual groups performing the exercise had difficulties identifying any potential failure mode for particular steps of the process. The sense was conveyed among the teams that the exercise, when performed in this way, was not value adding, as it was not clear whether the methodology was being applied to what was important or not. It became evident fairly early in the Workshop that this approach was not working, and that applying the methodology in this way was not an optimum use of the methodology, or the personnel resources involved.

Workshop No. 2 and No. 3 were run differently. Here, the aim was to apply the methodology to a smaller number of potential failure modes, whilst ensuring that the potential failure modes identified were sufficiently important to merit their evaluation via this formal and rigorous Quality Risk Management methodology. Thus, in contrast to the first workshop, the methodology was applied at a higher indenture level in the items under study. In this regard, the teams took a step back and viewed the item under study from a more general, holistic perspective, to determine what could go wrong in the manufacturing processes under study. Importantly, the learnings gained from Workshop No. 1 in relation to the procedures for identifying and documenting potential Failure Modes, and for brainstorming activities in general, were taken into account, and these learnings were found to have been beneficial.

In Workshop No. 2, a loss of yield of the API during drying was one of the potential failure modes identified for formal evaluation via the Quality Risk Management methodology. In Workshop No. 3, the non-aseptic transfer of the bioreactor inoculum from a small volume bioreactor to a larger volume bioreactor was one of the potential failure modes identified for evaluation. These represented relatively 'high level' potential failure modes in the processes under study. While difficulties (as described earlier in this chapter and as documented in the February 2007 issue of the Journal of Validation Technology) were identified during Workshop No. 2 in relation to how the

potential failure modes had been identified and documented, the above approach was observed to be useful and beneficial.

Overall, in the latter two workshops, a smaller number of potential failure modes were identified and evaluated in comparison to Workshop 1. It was clear, however, that these were more important from a risk perspective, and that the Quality Risk Management methodology had been applied in a manner that was more value-adding and meaningful than in Workshop No. 1. Given the rigorous and systematic nature of this methodology, it was found that investigating a small number of important potential failure modes was a more appropriate use of the methodology than applying the methodology to a large number of potential failure modes. In addition, it was found that it was more beneficial to identify potential failure modes at a relatively high indenture level in the item under study rather than at a much lower indenture level in the item under study.

From discussions with the team participants who performed the Quality Risk Management exercises, it was evident that, in the latter two workshops, the methodology had been applied to the more important potential failure modes in the items under study. Also, when applied in this way, the methodology was found to be more value adding and made a more efficient use of the personnel resources involved.

It was becoming evident that this methodology, as a formal, rigorous and systematic approach to Quality Risk Management, was probably best suited to evaluating and addressing the highest priority/most important potential Failure Modes, and that the use of this methodology should be commensurate with the complexity and/or criticality of the issue to be addressed.

This is in accordance with the guidance presented in ICH Q9, which states that the level of effort, formality and documentation of the Quality Risk Management process should be commensurate with the level of risk, and that the degree of rigor and formality of Quality Risk Management should be commensurate with the complexity and/or criticality of the issue to be addressed.

2.3.4.8 Results for Key Research Question No. 5

Key Question 5 was as follows:

- *Apart from general training activities on the Quality Risk Management methodology, what features of the methodology require special attention and guidance when developing training materials for users of the methodology?*

Several areas and features of this Quality Risk Management methodology were found during the above workshops to require detailed training activities and materials, and which were observed to be especially prone to problems of subjectivity and uncertainty.

These included:

- The identification and documentation of potential Failure Modes;
- The estimation of the probability of occurrence associated with the causes of potential failure modes;
- The estimation of the severity of the effects associated with potential failure modes
- Carrying out team-based activities (such as brainstorming during the identification and documentation of potential Failure Modes) during Quality Risk Management exercises;
- Assembling comprehensive data on the Item under Study prior to the start of the Quality Risk Management exercise;
- How the methodology deals with GMP controls during Quality Risk Management exercises, and how controls are classified in terms of how they relate to the severity, probability of occurrence and detection of a potential failure mode;
- Risk Communication activities.

See Chapter 6 of this thesis for a detailed discussion on the training requirements which have been identified for users of this Quality Risk Management methodology.

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Chapter 3

Generation, testing and evaluation of Version 2 of the Quality Risk Management Methodology

3.1 Introduction & Generation of Version 2 of the Quality Risk Management Methodology

All of the learnings identified during the series of practical GMP-related workshops, as discussed in Chapter 2, were compiled and evaluated, and a number of required design and process modifications to Version 1 of the Quality Risk Management methodology were identified and implemented. Thus, Version 2 of the methodology was generated.

The components of the methodology that were modified were a) the five stage process used by the Quality Risk Management methodology, b) the Worksheet used by the methodology, and c) the Risk Table. Each of these modifications is described in detail below.

3.1.1 Quality Risk Management Process Modifications

The Quality Risk Management process was redesigned from the relatively simple five stage process used by Version 1 of the methodology, (as documented in Chapter 2, Section 2.3.1.2), into one which contained two main sections, A & B, and thirteen individual process stages, A1 through A7, and B1 through B6.

Section A of the revised process related to the *preparatory activities* required for carrying out a Quality Risk Management exercise with this methodology, and was divided into seven *process stages,* as documented in Table 3.1 below.

Section B related to the *actual execution* of the Quality Risk Management exercise. This comprised of six individual *process stages,* beginning with the Risk Assessment activities, and these are documented in Table 3.2 below.

Table 3.1 The revised Quality Risk Management process

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
A1	***Defining & Describing the Item under Study in the Quality Risk Management*** This stage involved: ➢ Documenting what the methodology was being applied to (e.g. a manufacturing process, a utility system). ➢ Documenting specifically what the Item under Study was. ➢ Assembling comprehensive information and data on the Item under Study. ➢ Describing the proposed change, in cases where the Item under Study was a Change Control proposal. ➢ Documenting the scope and boundary of the Quality Risk Management exercise.

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
A2	***Defining the Nature & Purpose of the Quality Risk Management Exercise*** This stage involved: ➢ Documenting whether the nature of the exercise was a Prospective or Retrospective application of the Quality Risk Management methodology. ➢ Documenting whether the nature of the exercise was a Change Control Proposal evaluation. ➢ Documenting the exact purpose of the exercise (e.g. to help determine prospectively the scope and extent of Qualification & Validation requirements for a new Manufacturing Process, or to help identify, evaluate and manage risks associated with a proposed Change in a item of equipment). ➢ Describing any problem issue that had triggered the Quality Risk Management exercise.

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
A3	***Assembling & Defining the Quality Risk Management Team to carry out the Quality Risk Management exercise*** This stage involved: ➢ Identifying & assembling the necessary individuals required to make up the Quality Risk Management team. ➢ Documenting the name and position/area of expertise of each individual on the team. ➢ Documenting the name and position/area of expertise of the Team Leader for the Quality Risk Management exercise. * The term *Position* here referred to the position of the individual in the company or organisation in which the Quality Risk Management exercise was being performed.

Table 3.1 Cont'd

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
A4	***Reviewing (and modifying, where necessary) the Probability of Occurrence Levels used by the methodology*** This stage involved: ➢ Reviewing the four Probability of Occurrence levels (Likely, Occasional, Unlikely, Remote) and the default definitions associated with each level. These are used when estimating the risk associated with potential Failure Modes. ➢ Deciding whether the aforementioned default definitions of the various Probability of Occurrence levels needed any modification taking into account the Quality Risk Management exercise at hand. ➢ Documenting any revisions made by the Quality Risk Management team to the default definitions provided for the various Probability of Occurrence levels.

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
A5	***Identifying the stakeholders associated with the Item under Study, and reviewing (and modifying if necessary) the Severity Levels used by the methodology*** This stage involved: ➢ Identifying and documenting the Stakeholder groups associated with the Item under Study in the Quality Risk Management exercise. (For example, Stakeholders might include patients, or a specific customer, or the Company itself, from a regulatory compliance status, reputation, business perspective, etc.). ➢ Reviewing the three Severity levels (Critical, Moderate, Minor) provided by the methodology, as well as the default definitions associated with each level. These are used when estimating the risk associated with potential Failure Modes. ➢ Deciding whether any additional criteria are required with respect to any of the three Severity levels, taking into account the Stakeholders associated with the Quality Risk Management exercise, and the nature of the exercise at hand. ➢ Documenting any additional criteria that were determined as being required with respect to any of the three Severity levels.

Table 3.1 Cont'd

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
A6	***Reviewing the Risk Table used by the methodology*** This stage involved: ➢ Reviewing the structure and content of the Risk Table, which is a matrix of the Probability of Occurrence and Severity levels used during the Risk Assessment stage of the exercise. ➢ Reviewing the definitions provided with the Risk table for the terms *Intolerable, Unacceptable* and *Acceptable*. These terms are labels that are applied to certain risks, as defined by the Risk table. ➢ Reviewing the guidance provided with the Risk Table on the generally required actions that are associated with the three types of Risk – Intolerable Risk, Unacceptable Risk and Acceptable Risk.

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
A7	***Reviewing (and modifying where necessary) the Detection Levels used by the methodology*** This stage involved: ➢ Reviewing the four Detection levels (High, Medium, Low, None) and the default definitions associated with the four levels. These are used when assessing the usefulness of detection-related controls in risk control or mitigation, following the Risk Assessment part of the exercise. ➢ Deciding whether the default definitions for the various Detection levels require any modification taking into account the Quality Risk Management exercise at hand. ➢ Documenting any revisions made by the Quality Risk Management team to the default definitions provided for the various Detection levels.

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
B1	***Risk Assessment Part 1- the Failure Mode Identification process*** This stage involved: ➢ Carrying out brainstorming and/or data review activities in order to identify potential Failure Modes for the Item under Study. (These activities are executed by the multi-disciplinary Quality risk management team performing the Quality Risk Management exercise.) ➢ Documenting the potential Failure Modes identified for the Item under Study. ➢ Compiling data and/or reports in relation to each potential Failure Mode identified, and making a reference to such information on the Worksheet.

Table 3.1 Cont'd

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
B2	***Risk Assessment Part II – the Risk Evaluation process*** This stage involved: ➢ Using the brainstorming and data review activities from Stage B1 to identify the potential consequences of each Failure Mode identified for the Item under Study. ➢ Assessing and documenting any currently-in-place controls associated with the item under study which may serve to limit the severity of the effects of each potential Failure Mode, after the potential Failure Mode has occurred. ➢ Critically evaluating the usefulness of any such controls, and assigning a Severity rating to the potential consequences of the potential Failure Mode, taking into account the controls in question. ➢ Identifying the causes (or mechanisms) by which each potential Failure Mode may occur. ➢ Assessing and documenting any currently-in-place preventative controls or other measures which may serve to prevent or limit the probability of occurrence of the cause of each potential Failure Mode. ➢ Critically evaluating the usefulness of any such preventative controls and measures, and assigning a Probability of Occurrence rating to each potential cause of the potential Failure Mode, taking into aceount the controls in question. ➢ Using the Severity and Probability of Occurrence ratings, and the Risk Table from Section A6, to estimate and assess the risk associated with the cause of each potential Failure Mode. The Risks will either be considered Intolerable, Unacceptable, or Acceptable using this approach. ➢ Where a risk is deemed Intolerable or Unacceptable, the team considers, documents and critically evaluates what, if any, detection controls are currently in place that may serve to detect the potential failure mode, its cause, or its consequences, after the potential failure mode has occurred. ➢ Assigning a **detection rating** to the detection controls that are in place, and evaluating whether the detection controls in question give **adequate assurance** that the risk in question is adequately controlled, and that no further risk mitigating controls are required. (This step is carried out regardless of the detection rating assigned to the controls that may be in plaee.) ➢ Where the team considers that the detection controls in question do give adequate assurance that the risk is adequately controlled and that no further risk mitigating controls are required, the team proceeds to Stage B4 below, relating to Critical Process Parameters and Qualification & Validation Requirements. ➢ Where the team considers that the detection controls in question do not give adequate assurance that the risk is adequately controlled, the team proceeds to the Risk Control part of the process, Stage B3.

Table 3.1 Cont'd

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
B3	***Risk Control activities*** This stage involved: ➢ Identifying any risk control measures for each Intolerable or Unacceptable risk, that may serve to reduce the risk to an acceptable level, or that may serve to control the risk to an acceptable degree. ➢ In this regard, new controls which may serve to limit the severity of the effects of the potential Failure Mode are identified, documented and critically evaluated, as described above in Section B2, and a revised Severity rating is assigned to the potential Failure Mode, taking into account the new controls identified above. ➢ Also, new controls which serve to reduce the probability of the cause of the potential Failure Mode occurring are documented and critically evaluated, as described above in Section B2, and a revised Probability of Occurrence rating is then assigned to the cause of the potential Failure Mode, taking into account the controls identified above. ➢ The relevant steps described above in the Risk Assessment Section B2 are repeated, and Risk Control activities continue until either the risk in question can be considered acceptable by the team, on the basis of the risk control measures, or, in the case of risks that are still considered Intolerable or Unacceptable, that the risk is considered to be adequately controlled on the basis of new detection controls. The steps outlined above in Section B2 are followed in making this decision. ➢ Where the risk in question is either acceptable or under sufficient control that there is adequate assurance that no further risk mitigating controls are required, the team proceeds to Stage B4 below. This relates to Qualification & Validation Requirements.

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
B4	***Identification of Qualification & Validation status and related Requirements*** This stage involved: ➢ Identifying, for each control determined to be useful in risk mitigation and/or control, the items (such as documentation, equipment, facilities, personnel resources, etc.), that are required for the control to be in place. ➢ Determining and documenting whether such items are already in place or not. ➢ Determining and documenting whether each control has any associated Critical Process Parameters (CPPs) to be measured or monitored. ➢ Listing the Critical Process Parameters and the associated limits or acceptance criteria. ➢ Determining and documenting whether there are any other acceptance criteria or required outcomes for each control. ➢ Determining if the control has been or needs to be captured in a Qualification or Validation exercise, and describing that Qualification or Validation exercise. ➢ Documenting the Qualification or Validation status of the control in question, and documenting whether any new Qualification or Validation work is required.

Table 3.1 Cont'd

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
B5	***Defining the Action Items arising from the Qualification & Validation section*** This stage involved: ➢ Documenting all action items arising out of the Quality Risk Management exercise. (These could be actions required to implement a control, or they could be Qualification or Validation exercises.) ➢ Assigning personal or group responsibilities for each action item. ➢ Agreeing on, and assigning, a specific target completion data for each action item.

Process Stage	Required Activity for this Stage of the Quality Risk Management Process
B6	***Communication & Periodic Review Activities*** This stage involved: ➢ Reviewing and documenting what, if any, risk communication activities are required arising out of the Quality Risk Management exercise, with respect to any of the risks identified during the exercise, or the control strategies associate with any risk. ➢ Assigning personal or group responsibilities for each communication activity. ➢ Agreeing on, and assigning, a specific target completion data for each communication activity. ➢ Deciding and documenting when the Quality Risk Management exercise should be reviewed. ➢ Discussing and agreeing who should perform the review exercise. ➢ Closing out the Quality Risk Management exercise.

While the above Quality Risk Management process was longer and more comprehensive in detail than that used by Version 1 of the methodology (as documented in Chapter 2, Section 2.3.1.2), the fundamental features and key features of both versions remained unchanged. Thus, each process was designed to be team-based, there was a high emphasis on GMP controls and the qualification and validation requirements for such, and each version required detailed Risk Assessment, Risk Control, Risk Review and Risk Communication activities to be undertaken.

However, the process used by the Version 2 of the methodology differed in two important ways from the process used by Version 1.

The first difference related to the first stage of the Quality Risk Management process, which had been modified in Version 2 to require the team to acknowledge and document in sufficient detail all of the pertinent assumptions that were relevant to the exercise at hand. For example, assumptions in relation to the qualification status of the equipment used in manufacturing process under study, or in the level of training given to staff members at the time of the Quality Risk Management exercise, were now to be explicitly documented during the exercise, and the Worksheet used by this Quality Risk Management methodology was revised to specifically accommodate this new requirement.

The second change related to how the Quality Risk Management process dealt with the nature and purpose of the Quality Risk Management exercise at hand. In Version 2 of the methodology, the Quality Risk Management process required the nature and purpose of the exercise to be explicitly documented by the team performing the exercise, and to be reviewed at the outset of the exercise. Again, the Worksheet provided with Version 2 of the methodology had been revised to accommodate this new requirement.

3.1.2 Quality Risk Management Worksheet Modifications

The Worksheet that had been developed for Version 1 of the Quality Risk Management methodology was completely redesigned and restructured as a result of the revisions made to the Quality Risk Management process used by the methodology, when Version 2 of the methodology was being developed.

The first main change was to directly reflect the various stages of the revised version of the Quality Risk Management process used by Version 2 of the methodology. Thus, the Worksheet was now structured into two main Sections, A & B, with Section A addressing the preparatory activities for the Quality Risk Management exercise at hand, and Section B addressing the actual execution of the exercise, starting at the Risk Assessment part of the process. Thus, the revised Worksheet now had thirteen individual stages, (seven devoted to Section A of the process, and six devoted to Section B).

The second main change made to the Worksheet was to explicitly incorporate into the design of the worksheet many additional elements of the Quality Risk Management process that were absent from the first version of the Worksheet. For example, the revised Worksheet required significantly more information to be recorded and compiled on the Item under Study and on the exercise at hand than the worksheet used in Version 1 of the Quality Risk Management methodology. In Section A2, there was now a requirement to more clearly define the nature and purpose of the exercise at hand. In Section B4, requirements in relation to Qualification and Validation were given greater focus and rigor, and the Qualification and Validation *status* of each control was now required to be established and documented.

In addition, the qualification and validation activities documented in Section B4 were now more explicitly linked to the GMP controls that were documented in earlier Sections of the worksheet. While this had been a feature of the previous version of the worksheet, it was made more transparent with the generation of version 2. In Section B6, there was now a formal requirement to document risk communication activities for the outcomes of the Quality Risk Management exercise, and to document and plan for periodic review activities. These had not formally been included in the worksheet from Version 1 of the methodology.

In overall terms, this version of the worksheet was more comprehensive in scope and required a much higher level of detail to be recorded in almost all areas. Notes pages were also incorporated into the design of the worksheet, to enable notes to be made by the team performing the Quality Risk Management exercise. The design and structure of the revised Worksheet are shown in Section 3.1.2.1, below.

3.1.3 Modification of the Risk Table used by the methodology

As explained in detail in Chapter 2, during the testing and evaluation of Version 1 of the Quality Risk Management methodology, a fault was identified in the design of the Risk Table provided with Version 1 of the methodology.

This resulted in the modification of the Risk Table with respect to how potential failure modes, which had been assigned a remote Probability of Occurrence and a Critical

Severity rating, were categorised by the Risk Table. The new version of the Risk Table, as explained in Chapter 2, categorised such risks as being acceptable. The revised Risk Table is shown above in Section A6 of the Worksheet, below.

3.1.2.1 Revised Worksheet for Version 2 of the Quality Risk Management methodology

GMP Risk Management Exercise - Overview

Risk Management (RM) Exercise No: _____

Title of Exercise: _____

Start Date: _____ Location: _____

***Instruction**: The Tables below allow for tracking the progress of the RM exercise. Tick each Section in the Table below when completed.*

Section A – Preparation		
Section No.	**Topic**	**Section Status**
A1	Preliminary Information: o Item Under Study o Details of the Item Under Study	❑ Completed
A2	Purpose of this RM Exercise: o Prospective Risk Management Exercise o Retrospective Risk Management Exercise o Change Control Evaluation	❑ Completed
A3	Risk Management Team	❑ Completed
A4	Probability Level Table	❑ Completed
A5	Stakeholders & Severity Level Table	❑ Completed
A6	Risk Table	❑ Completed
A7	Detection Control Table	❑ Completed

Section B – Execution		
Section No.	**Topic**	**Section Status**
B1	Risk Assessment Part 1- Failure Mode Identification	❑ Completed
B2	Risk Assessment Part II - Risk Evaluation	❑ Completed
B3	Risk Control	❑ Completed
B4	Qualification & Validation	❑ Completed
B5	Action Items	❑ Completed
B6	Communication & Periodic Review Activities	❑ Completed

Section A1: Preliminary Information

Instruction: Complete the Following Tables:

Item Under Study
What is this RM Tool being applied to? *Tick one or more of the following Items:* ❑ A Manufacturing Process ❑ A Cleaning Process ❑ An Item (or Train) of Equipment ❑ A Utility System (e.g. compressed air, purified water, etc.) ❑ Other Type of System (e.g. a Building Management System, a Supplier Approval System, a Regulatory Complianee System): specify: _____ _____ _____ ❑ A Change Control ❑ A Specific Issue or Problem which has been identified & which may impact upon Qualification/Validation Status

Details & Comprehensive Description of the Item Under Study: Attach compiled documentation	
Name of the Item Under Study (e.g. Manufacturing Process for Product X, or Change Control No. 1234, or Room No ABC)	
Reference Number or Document Number (if any) associated with the Item Under Study:	
For a Change Control: Description of the Proposed Change CC Ref. Number: _____	
<u>Scope & Boundary</u> State the Start and End points for this RM Exercise, or the items which come within the scope of this exercise:	
If this RM exercise applies only to a part of the Item Under Study (e.g. the drying & discharge stage in an API manufacturing process), then: • Clearly state the stage or part of the Item Under Study: • State the start and end points of the stage or part of the Item Under Study:	

Section A2: Purpose of this RM Exercise

Instruction: Tick the Options below which best describe the purpose of this exercise, and complete the relevant Tables below:

❑ Option 1 – This is a **Prospective Risk Management Exercise**

The tool is being used in order to help determine prospectively the scope and extent of Qualification & Validation reqnirements for a uew or to be changed: (tick one)

- ❑ Mannfacturing Process
- ❑ Cleaning Process
- ❑ Item, or Train, of Equipment
- ❑ Utility System (e.g. compressed air, purified water, etc.)
- ❑ Orher Type of Systern (e.g. a Building Management System, a Supplier Approval System, a Regulatory Complianee System): specify: _____

Note: For Change Controls, the tool is also designed to help identify, evaluate and manage risks associated with the Change. If this is required, tick option 3 below also.

❑ Option 2 – This is a **Retrospective Risk Management Exercise**

The tool is being used in order to help determine retrospectively the Qualification & Validation status of, and the Qualification & Validation requirements for: (tick one or more)

- ❑ A Manufacturing Process
- ❑ A Cleaning Process
- ❑ An Item, or Train, of Equipment
- ❑ A Utility System (e.g. compressed air, purified water, etc.)
- ❑ Other Type of System (e.g. a Bnilding Management System, a Supplier Approval System, a Rcgnlatory Compliance System): specify: _____

❑ If the RM exercise is to help determine retrospectively Qualification & Validation status in response to a **specific issue or problem** (e.g. a series of batch rejects), briefly state the problem here:

Specific issue or problem:

❑ Option 3 – This is a Risk Management Exercise to Evaluate a Change Control Proposal

The tool is being nsed in order to help identify, evalnate and manage risks associated with a proposed Change associated with: (tick one)

- ❑ A Manufaeturing Process
- ❑ A Cleaning Process
- ❑ An Item, or Train, of Equipment
- ❑ A Utility System (e.g. eompressed air, purificd water, etc.)
- ❑ Other Type of System (e.g. a Building Management Systern, a Supplier Approval System, a Regulatory Complianec System): speeify: _____

Section A2 Cont'd

Instruction: Add any other information regarding the purpose of this Risk Management Exercise in the Table below.

Other Information:

Section A3: Risk Management Team

Instruction. *List the individuals who will make up the RM Team, together their positions and areas of responsibility:*

Name of RM Team Leader: _____

Position / Area of Expertise: _____

Other Team Member Name	Position / Area of Expertise

Notes:

Section A4: Probability of Occurrence of Failure Modes Table

There are four Probability Levels: **Likely, Occasional, Unlikely, Remote**

Instruction: Each Probability Level is defined in the table below. However, if considered necessary, further define the Probability in the spaces provided, as appropriate for this RM Exercise:

P - Probability Level Table
Likely: The Failure Mode is Likely to Occur ***Optional***: Define Any Other Criteria for this Probability Level here: (e.g. in more than 20% of the time; everyday; every time the action is executed, or, every batch, etc.)
Occasional: The Failure Mode May Occur ***Optional***: Define Any Other Criteria for this Probability Level here: (e.g. 5 - 20% of the time; or, once per week; or, every 10th batch, etc.)
Unlikely: The Failure Mode is Unlikely to Occur ***Optional***: Define Any Other Criteria for this Probability Level here: (e.g. 1 - 5% of the time; or, once per quarter; etc.)
Remote: The Failure Mode is Very Unlikely to Occur ***Optional***: Define Any Other Criteria for this Probability Level here: (e.g. less then 1% of the time; or, once per year; etc.)

Notes:

Section A5: Stakeholders & Severity Level Table

Instruction: *Identify the Stakeholders who are associated with the Item Under Study in this RM Exercise. For example, Stakeholders might include patients, or a specific customer, or the Company itself, (e.g. from an economics, regulatory compliance status, reputation perspective).*

Record Stakeholder Groups Here:

There are three Severity Levels used in this RM Tool: **Critical, Moderate & Minor**.

Instruction: *Select or define any specific criteria within each Severity rating below which are relevant to this Risk Assessment exercise and to the Stakeholders:*

S - Severity Level Table
Critical: The Effects of the Failure Mode are considered to be Critical in Severity ❑ Very Significant Non-Compliance with GMP or the MA ❑ Patient Injury ❑ Other: _____ ❑ Other: _____ ❑ Other: _____
Moderate: The Effeets of the Failure Mode are considered to be Moderate in Severity ❑ Significant Non-Compliance with GMP or the MA ❑ Patient Impact ❑ Other: _____ ❑ Other: _____ ❑ Other: _____
Minor: The Effects of the Failure Mode are considered to be Minor in Severity ❑ Minor Non-Complianee with GMP or the MA ❑ No Patient Impact or Injury ❑ Other: _____ ❑ Other: _____ ❑ Other: _____

Notes

Section A6: Risk Table

The Table below shows how to estimate the Risk associated with each Failure Mode (Risk = P x S)

***Instruction**: None. This section is for information*

Risk Table			
Failure Mode	*Minor Severity*	*Moderate Severity*	*Critical Severity*
Likely	**Unacceptable**	**Intolerable**	**Intolerable**
Occasional	**Acceptable**	**Unacceptable**	**Intolerable**
Unlikely	**Acceptable**	**Acceptable**	**Unacceptable**
Remote	**Acceptable**	**Acceptable**	**Acceptable**

Risk Definitions:
Intolerable - The Risk is Intolerable Eliminate the Failure Mode or build in systems/controls to ensure the effects of the Failure Mode are not realised (e.g. via redundant systems) **Unacceptable** - The Risk is Unacceptable The Risk for this Failure Mode must be Reduced or Controlled to an Acceptable Level **Acceptable** - The Risk is Acceptable No Risk Reduction or New Controls are Required

Notes:

Section A7: Detection Controls Table

There are four Detection Control Levels available to choose from, when rating Detection Controls. These are: **High, Medium, Low & None.**

***Instruction**: Insert any special detection criteria in the spaces provided below, which may be appropriate to this Risk Assessment exercise.*

D - Detection Control Table
High: There is a High Likelihood that Controls will Detect the Failure Mode or its Effects after the Failure Mode has occurred Special Detection Criteria:
Medium: There is a Medium Likelihood that Controls will Detect the Failure Mode or its Effects after the Failure Mode has occurred Special Detection Criteria:
Low: There is a Low Likelihood that Controls will Detect the Failure Mode or its Effects after the Failure Mode has occurred Special Detection Criteria:
None: Detection Controls are Absent

Notes:

Section B – Execution of the Risk Management Exercise

Note: Section B is comprised of six separate parts, as described below.

***Instruction**: None. This is for information purposes.*

Overview of Section B

Section B1: Risk Assessment Part I - Failure Mode Identification

- This Worksheet lets us record the Failure Modes which were identified via the Data Review and Brainstorming Session

Section B2: Risk Assessment Part II - Risk Evaluation

- This Worksheet lets us Estimate the risk(s) associated with each Failure Mode
- This Worksheet allows us to decide whether each risk is acceptable, adequately controlled or not adequately controlled
- One Worksheet is used per Failure Mode

Section B3: Risk Control

- This Worksheet is used to control each risk associated with the Failure Mode in question
- The Worksheet is only used for risks which are not adequately controlled
- One worksheet per risk… so, one Failure Mode with multiple risks will have several of these B3 worksheets associated with it, if the risks are not adequately controlled

Section B4: Qualification & Validation

- This Worksheet takes each control in turn and identifies any items needed to implement the control
- The Worksheet applies both to existing controls (i.e. which are currently in place), and to new controls
- For each control, this Worksheet lets us determine any Qualification & Validation requirements
- One worksheet per control…. so, one Failure Mode with multiple controls will have several of these B4 worksheets

Section B5: Actions

- This Worksheet allows us to compile action items arising from the Risk Management

Section B6: Communication & Periodic Review Activities

- This Worksheet allows us to identify risk communication requirements and it allows us to plan for Periodic Review Activities

Notes:

Section B1: Risk Assessment Part 1 - Failure Mode Identification

***Instruction**: Complete the Following Parts and Table.*

Data Review & Brainstorming Session No: _____ ____ Session Date: __ _____

Initials of RM Team Members Present: _ _____ _____ ____ _____ ____

Failure Modes Identified		
No.	Failure Mode	Reference, Comments
1		
2		
3		
4		
5		

Section B1, Cont'd

Instruction: *Record additional Failure Modes here*

Failure Modes Identified		
No.	Failure Mode	Reference, Comments
6		
7		
8		
9		
10		

Section B2: Risk Assessment Part II - Risk Evaluation

***Instruction**: Complete the tables below. Use a Separate Section B2 for each Failure Mode*

Failure Mode	
No.	Failure Mode Description & Reference to Process Stage

Potential Effects of this Failure Mode:	Controls in place which reduce or eliminate the effects after the failure mode has occurred: *(These are Severity Controls)*	S: Overall Severity Rating Crit/Mod/ Min
Overall S =		

Causes or Mechanisms for this Failure Mode to Occur: *(Number each starting with No. 1)*	Current Preventative Controls in place: *(List the controls for each individual Failure Mode Cause or Mechanism)*	P: Prob. of Occur of F Mode	**Risk = P x S (See table)**
#			

For Acceptable Risks, Go to Section B4. For all other Risks, Continue with Section B2 (Next Page)

Section B2, Cont'd:

Instruction. *This section is for Unacceptable or Intolerable Risks Only: Complete the table below.*

Detection Controls			
Risk No	List any Detection Controls currently in place (& not already listed above) which detect the Failure Mode or its effects after it occurs	D Rating: Low/Med /High	Decision Point Is this Risk adequately controlled* - Yes / No (Insert any relevant explanation here)

* i.e. Do these detection controls **give assurance** that the risk is adequately controlled & that no further controls are required? If Yes, Go to Section B4; if No, Go to Section B3.

Section B2 Cont'd – Notes & Comments Page

Instruction: *Use this sheet to record any important notes or explanatory comments pertaining to the Risk Evaluation stage.*

Give a reference in the left column for the note or comment. For example, if the note or comment relates to a Preventative Control in Section B2, indicate that in the Reference column.

Reference	Note / Comment

Section B3: Risk Control
***Instruction**: For Intolerable / Unacceptable Risks not adequately controlled. One sheet per Risk!*

Failure Mode No:	**Risk No.**	**Risk**: ❑ Unacceptable ❑ Intolerable
Failure Mode Cause or Mechanism (from Section B2):		

Risk Reduction Measures

What **new Preventative Controls** could be put in place which would prevent the above Failure Mode cause or the mechanism for the Failnre Mode? P =	**New Probability P** Rating for this Failure Mode
What **new Controls** could be put in place to reduce or eliminate the effects of this failure mode <u>after</u> it has occurred? (These are called Severity Controls) S =	**New Overall Severity S Rating** for these Effects

New Risk =

❑ **Acceptable** - go to Sheet B4
❑ **Unacceptable / Intolerable** - continue below

If the Risk is still Unacceptable or Intolerable:

What **new Detection Controls** could be put in place which would detect the above F. Mode?	New D Rating: Lo/Med/ Hi	Decision Point: Is the risk now adequately controlled? * Yes / No. Comment/Explain

** i.e. Do these measures now ensure that the Risk is either reduced to an acceptable level or adequately controlled? If Yes, Go to Section B4. If No, then repeat this sheet before continuing on to Section B4*
Note: if any of the above new controls may introduce any new risk, complete a new Section B2

Section B3 Cont'd – Notes & Comments Page

Instruction: *Use this sheet to record any important notes or explanatory comments pertaining to the Risk Control stage*

Reference	Note / Comment

Section B4: Qualification & Validation

Instruction: Complete one worksheet for each control as identified in Sections B2 & B3

Failure Mode Ref. No.	**Type of Control:** ❑ Current Control ❑ New Control
Brief Description of the Control:	

Required Items for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

If these items are **Already In Place**, tick here: ❑

Critical Process Parameters (CPPs):

Does this control have any associated CPPs to be measured or monitored? ❑Yes ❑ No

If yes, list the CPPs below:	If yes, specify the Limits or Acceptance Criteria

Are there any Other Acceptance Criteria or Required Outcomes for this Control? ❑Yes ❑ No

If yes, specify these here:

Qualification & Validation requirements associated with this control:

If this control has been or needs to be captured in a Qualification or Validation exercise, describe the Qualification or Validation exercise here:	Q/V Exercise Status: ❑ Completed ❑ Not Completed ❑ N/A

Current Qualification or Validation Status? (Tick one below)

❑ New Qualification/Validation work needed ❑ No New Qualification/Validation work needed

Section B4 Cont'd – Notes & Comments Page

Instruction: *Use this sheet to record any important notes or explanatory comments pertaining to the Qualification & Validation stage*

Reference	Note / Comment

Section B5: Actions

Instruction: *Complete this Section by identifying action items from the Qualification & Validation Worksheets*

Action Items *Note: these could be actions required to implement a new control, or a Qualification or Validation Exercise*			
F. Mode No.	Action Item:	Responsible Person / Group	Target Date for Completion

Section B6: Communication & Periodic Review Activities

***Instruction**: Complete this Section by identifying communication activities for risks, and periodic review requirements for the Risk Management exercise*

Communication Requirements:

List any communication activities required in order to communicate risks to key groups or stakeholders

Communication Activity & Method:	Responsible Group	Target Date for Completion

Periodic Review Activities:

State the date the Risk Assessment will be reviewed: _____

Proposed Reviewing Team Members: _____

Close Out

Date this RM Exercise is being closed out: _____

By Whom: _____

Comments: _____

Filing/Copying Instructions:

3.2 Research Methods & Key Research Questions for the Testing and Evaluation of Version 2 of the methodology

Following the development of Version 2 of the methodology, testing and evaluation activities on this version were initiated. The research methods used in this regard, and the key research questions to be addressed during this testing and evaluation phase, are discussed below.

3.2.1 Challenging the Methodology with two new GMP-related Case Studies

Two new GMP-related case studies were developed and processed through Version 2 of the Quality Risk Management methodology. This was in order to challenge the design and structure of the methodology in two quite differing areas:

- Supplier and material approval activities at a manufacturer of a new investigational medicinal product *(Case Study 3)*

- Material dispensing activities at a manufacturer of solid oral dose medicinal products *(Case study 4)*

The above areas were selected because they related to specific real-life GMP problems and concerns that had been identified during GMP-related regulatory activities, as discussed below. The Case Studies were designed to evaluate how applicable the methodology was when applied to such different areas and activities within the GMP environment, and to identify any faults in the methodology that needed to be corrected.

The following is an outline of each of the two new Case Studies. (As these are the third and fourth Case Studies presented in this thesis, they are numbered Case Study 3 and Case Study 4.)

3.2.1.1 Case Study 3: Supplier and Material Approval Activities

This Case Study related to potential use of a new supplier of a critical product-contact material used in the milling of an intermediate investigational medicinal product. It was based on real-life GMP issues that had been identified during a GMP inspection of a manufacturer located within the EU.

The manufacturing facility in question planned to use a new wet-milling process during the manufacture of an intermediate medicinal product. The milling process involved milling a liquid suspension in the presence of yttrium zirconium beads to achieve the desired particle size reduction for the material. The beads were a new product contact material for the facility, and would be purchased from a supplier in China.

Different grades of beads, (each with a different particle size profile) were required in the milling operation, and these were to be used in a particular, defined sequence. The particle size profile of the beads, and the sequence in which the different grades of beads were used in the milling profile had earlier been determined (via R&D process development work) to be critical in achieving the correct particle size reduction profile in the milled intermediate medicinal product.

The inspector had noted that only limited testing was planned for the bead material when shipments were received into the facility; this involved performing only identity tests on a reduced number of drums in each shipment. No particle size testing was planned to confirm the correct particle size profile of the beads in each drum. It was also noted that the supply route for the bead material was relatively complex. Three different companies were involved in the handling and labelling of this material before it reached the manufacturing facility in question. The three companies were:

- The manufacturer of the beads. (This was a company located in China.)
- A brokerage company in China that was responsible for the supply of the material to export customers, including other brokerage firms, and
- A brokerage company in Europe that held the rights for the distribution of the material within the EU.

During the inspection, the company stated that the manufacturer in China would be audited and qualified by the manufacturer of the intermediate medicinal product, as part of its supplier/material approval programme. The two brokerage firms involved in the onward supply of the drums had not been audited or qualified in any way, and no plans were in place to do so. It was not known at the time of the inspection whether these companies were involved in drum labelling activities, but it was suspected that the EU brokerage firm was.

The inspector was concerned by the fact that no assurance had been obtained that the labels on drums of different grades of bead material correctly represented the grade of material inside the drums, or even that the drums contained the correct bead material. It was suggested by the inspector that the level of qualification planned for the bead material and its supply was not adequate, given the potential for labelling to be performed by different companies on the drums of this material. The Inspector requested that additional work to be carried out by the company, in order to demonstrate that the bead material, when received, was fit for use, and to determine if the level of GMP control in place for the material was appropriate, or whether additional Risk Control or Qualification/Validation work was required.

During the Case Study, Version 2 of the Quality Risk Management methodology was applied to the use of the bead material at the facility. This resulted in the determination that the risk presented by using the bead material as received via the supply route (as outlined above) had not adequately been controlled. Additional GMP control measures and additional Qualification and Validation work were identified as being required. This Case Study is presented in Volume 2 of this thesis, as a component in the Training & User's Manual (discussed in Chapter 6) that has been developed on this methodology.

3.2.1.2 Case Study 4: Material Dispensing Activities

This Case Study related to the potential for cross contamination during starting material dispensing activities at a manufacturer of tablets. It was also based on GMP issues that had been identified during inspection of a manufacturer located within the EU.

The manufacturing facility in question had a dispensing room for active substances that contained several open dispensing booths in a row. These were used to dispense different API materials at the same time. Given the open design of the area, the potential for cross contamination during starting material dispensing activities was a concern of the Inspectors during a GMP inspection of the facility.

The Inspectors required additional work to be carried out by the company in order to demonstrate whether the containment controls in place gave adequate assurance that the potential for cross-contamination had been adequately addressed, and to determine if the level of GMP control in place for the issue was appropriate, or whether additional Risk Control or Qualification/Validation work was required.

During the Case Study, Version 2 of the Quality Risk Management methodology was applied to the dispensing of API starting materials in this type of facility, and it resulted in the determination that the risk presented by those dispensing activities in the facility in question had not adequately been controlled. Additional GMP control measures and additional Qualification and Validation work were identified as being required. Given the length of this thesis, and the fact that four detailed Case Studies from Chapter 4, as well as Case study 3 from this Chapter are presented in this thesis, this particular Case Study is not presented in this thesis, but is available upon request from the author.

This Case Study, together with Version 2 of the Quality Risk Management methodology on which it was based, were presented by the author at an international GMP conference in July 2005. The conference, titled '*Top 10 GMP Inspection Issues*', was hosted by the UK's Parenteral Society[6] in Cork, Ireland. This allowed the author to obtain feedback, from an industry perspective, on the methodology, as the conference was attended by technical staff members of fifteen Irish and UK pharmaceutical manufacturing companies.

During the conference, Version 2 of the Quality Risk Management methodology was described in detail. This was followed by working through the above Case Study with

[6] Note: The UK's Parenteral Society was re-named to the Pharmaceutical & Healthcare Sciences Society (PHSS) in November 2005.

the participants of the conference, in order to demonstrate the practical application of the methodology within the GMP environment. An open discussion on the methodology and on the Case Study took place following the presentation.

A number of useful comments were made by the attendees of the conference on the Quality Risk Management methodology. While many of the comments were of a positive nature, several comments indicated that the methodology could be improved upon in several ways.

For the purposes of making improvements to the methodology as a result of the learnings gained from the conference, the points made in this regard during the conference were classified by the author as Faults in the methodology. These Faults are discussed in detail in the Results & Discussion section below. The improvements made to the methodology to correct each of the Faults identified are presented and discussed in Chapter 4 of this thesis, titled 'Generation, testing and evaluation of Version 3 of the Quality Risk Management Methodology.'

3.2.2 Key Research Questions to be addressed

Two key research questions were developed in order to help structure the above testing and evaluation activities for Version 2 of the Quality Risk Management methodology. These focussed on testing and evaluating the step-by-step process used by the methodology, and the design and structure of the components making up Version 2 of the methodology, particularly the tool worksheet and the supporting guidance documentation accompanying the worksheet.

The key research questions were as follows:

1. Are there any faults with the Quality Risk Management process used by this methodology, which might prevent the methodology from being a practical solution for determining, on a risk basis, the scope and extent of validation, and the likely impact of changes?

2. Are there any faults with the design and structure of the worksheet and other components making up the Quality Risk Management methodology, which might prevent this methodology from being a documented, scientific, practical, systematic, transparent, flexible, and ready-made solution to facilitate compliance with the EU GMP risk-based Qualification, Validation and Change Control requirements?

3.3 Results & Discussion

With respect to the Key Research Questions developed for this testing and evaluation stage, the results for each are presented below:

3.3.1 Results for Key Research Question No. 1

Key Question 1 was as follows:

- *Are there any faults with the Quality Risk Management process used by this methodology, which might prevent the tool from being a solution for determining, on a risk basis, the scope and extent of validation, and the likely impact of changes?*

Two main Faults were identified with the Quality Risk Management process used by this methodology.

Fault 1: The level of detail documented for the Quality Risk Management process

When working through Case Study No. 4 with the participants of the aforementioned international GMP Conference, it became evident that one of the key features of the methodology - the requirement to critically evaluate GMP controls prior to assigning any Severity, Probability of Occurrence or Detection ratings to a potential failure mode – had not clearly been reflected in the Quality Risk Management process documented for the methodology.

The questions received by the author during the seminar indicated that this feature of the methodology was not readily apparent to users of the methodology when working through the Risk Assessment and Risk Control steps of the process. These were sections B2 and B3 of the Worksheet associated with this version of the methodology. (See Section 3.1.2 above for an outline of the structure of the Worksheet.)

Fault 2: Assessment of the Qualification or Validation status of the Item under Study

It was noted that Section B6 of the Quality Risk Management process, titled 'Communication & Periodic Review Activities', did not clearly require any assessment of the Qualification or Validation status of the Item under Study.

This was a problem because maintaining control over the Qualification or Validation status of the Item under Study was one of the main reasons for incorporating Periodic Review activities into the methodology, yet the Quality Risk Management process did not give adequate attention to this important aspect of the methodology.

It was apparent also that the assessment of the Qualification or Validation status of the Item under Study needed to be documented more explicitly in the methodology.

3.3.2 Results for Key Research Question No. 2

Key Question 2 was as follows:

- *Are there any faults with the design and structure of the worksheet and other components making up the Quality Risk Management methodology, which might prevent this methodology from being a documented, scientific, practical, systematic, transparent, flexible, and ready-made solution to facilitate compliance with the EU GMP risk-based Qualification, Validation and Change Control requirements?*

Five individual faults were found with the design and structure of Worksheet which accompanied Version 2 of the methodology. These were as follows:

Fault 3: General Design of the Worksheet

When using the Worksheet with Case Studies 3 and 4, it was found that the Worksheet was generally of poor design. This was because the number of different Sections to be completed in the Worksheet, at thirteen, was found to be excessive, and the 21 pages making up the Worksheet rendered it too long to be practical or useable.

Several participants of the GMP Conference made observations in this regard also, stating that the length of the worksheet made it cumbersome and laborious to use and work through.

Fault 4: Guidance for the Failure Mode Identification step

During the review of Case Study 4 at the GMP Conference, it was observed that several participants had difficulty understanding how to complete Section B1 of the worksheet, which was titled '*Risk Assessment Part 1 – Failure Mode Identification*'.

The participants in question reported that this part of the Worksheet lacked clear guidance or instruction on what was required. For example, there was no guidance or instruction provided on approximately how many potential failure modes should be recorded in Section B1.

The Worksheet contained spaces for ten potential failure modes to be recorded in Section B1, but the author had stated during his presentation at the GMP Conference that this methodology was intended to be applied to a smaller number of potential failure modes, reflecting the learnings gained from the testing activities performed on Version 1 of the methodology. This also reflected the experience gained by the author when testing Version 2 of the methodology with the aforementioned Case Studies. This was found to be confusing for the conference participants.

During the conference, discussions in this regard were held between the author and several participants of the Conference who had expressed a particularly high interest in the methodology. One of the main points of discussion was the rigorous and technically detailed nature and scope of the methodology, and how the number of potential failure modes to be evaluated with the methodology might be restricted to a relatively small number to reflect this. There was general agreement from those participants that this approach was the best use of the methodology.

Fault 5: Guidance for documenting Specific Issues or Problems giving rise to the Quality Risk Management exercise

It was observed during two of the above Case Studies (No. 3 and No. 4) that the Worksheet was unclear in how Section B1 should be completed. This was for situations in which the Quality Risk Management exercise was being performed to address a specific issue or problem that had been identified with the Item under Study.

Section A1 of the Worksheet, titled '*Preliminary Information*' allowed the team performing the exercise to document that the exercise related to a specific issue or problem with the Item under Study, and in Section A2, titled '*Purpose of this Exercise*', a description of the specific issue or problem was to be documented.

However, when documenting potential failure modes in Section B1, it was observed that it was unclear what should actually be documented here: Should the specific issue

or problem be documented here as the potential failure mode, or should something else be documented? Thus, a fault was identified in this regard.

Fault 6: Structure of the Worksheet

When applied to each of the two new Case Studies, it was observed that the structure of the Worksheet was somewhat disjointed and cumbersome. This was in terms of how the default levels of Probability of Occurrence, Severity and Detection were presented in the Worksheet, and how these default levels were to be used in the Quality Risk management exercise. This same observation also applied to the Risk Table provided with the methodology.

While the default levels for Probability of Occurrence, Severity and Detection were clearly documented in the worksheet, in Sections A4 through A7, it became evident when using the worksheet that one needed to continuously revert back to those Sections for guidance on the default levels for Probability of Occurrence, Severity and Detection, and this interrupted the flow of work and the discussion taking place when working through other (later) Sections of the worksheet.

Fault 7: Documenting GMP Controls on the Worksheet

It was recommended during the GMP conference that Sections B2 and B3 of the Worksheet should be revised to more clearly describe the controls relating to the severity of the effects of a potential failure mode.

In this version of the Worksheet, these controls were termed 'Severity Controls'; they were described on the worksheet as 'controls which reduce or eliminate the effects after the potential failure mode has occurred'. Some of the conference participants, however, failed to understand the back-up and redundant nature of such controls, and they were confused as to what the term *Severity Control* actually meant.

The back-up or redundant nature of such controls was described verbally by the author during the presentation of the methodology at the Conference, but this was not documented on the worksheet, and a fault was identified in this regard.

It was noted that when the author verbally explained how Severity Controls were controls that could have a back-up or redundant nature, the conference participants

reported that this was useful in understanding the nature of those so-called 'Severity controls', and they recommended that this terminology be formally incorporated into the design of these Sections of the worksheet.

Other General Faults:

Three other faults were identified during this testing and evaluation stage with other aspects of the Quality Risk Management methodology. These related to:

- The lack of a documented training module on the methodology;
- The fact that there was no guidance provided for the handling of any disagreements in opinion documented which might occur over Probability of Occurrence and Severity ratings that were being assigned to a particular Failure Mode;
- The terminology used by the Quality Risk Management methodology.

Each of these faults is discussed in turn below.

Training Issues:

During discussions between the author and participants of the GMP conference, the most frequent questions on the methodology that were put to the author related to training activities, and whether a training module or programme had been developed for potential users of the methodology.

This indicated a generally high level of interest among the conference participants in learning how to use the methodology, but no documented training module or programme had yet been developed on the methodology. This was observed to be a drawback of the methodology at that time (July 2005).

Two main areas were identified as requiring specific training materials or guidance. The first related to demonstrating the meaning of Severity-related GMP controls. The second related to how the methodology addressed situations in which there was disagreement among team members when probability of occurrence and severity ratings were being assigned to a particular potential failure mode.

On a more general note, the discussions the author had with conference attendees indicated that when a training module was developed, it would be useful to include in it one simple, non-GMP related case study in order to demonstrate how the methodology works in its own right, without focussing on any GMP areas or issues.

In response to the above observations, a comprehensive training module was developed for potential users of this methodology. See Chapter 7 of this thesis in this regard.

Terminology Issues:

The term 'Severity Control' was observed to be difficult for users of the methodology to understand during the GMP Conference. This was despite the fact that explanatory text had been added to Quality Risk Management Worksheet in places where the term *Severity Control* was present, in order to clarify that these were controls which served to reduce or eliminate the effects of the Failure Mode, after the Failure Mode had occurred.

The term *Severity Control* had also been observed to be problematic during the testing of Version 1 of the methodology, as discussed in Chapter 2 of this thesis. It was therefore decided that this term should be removed completely from the methodology, and that it should be replaced by a term more intuitively easier to understand. The term *Severity Control* was eventually replaced with the phrase "Back-up Systems/Redundancy Controls", which, while longer in words, was preferable as it more accurately conveyed the exact role of the controls in question.

Disagreements in Opinion:

In relation to how disagreements in opinion over Probability of Occurrence and Severity ratings could be dealt with by this methodology, the author recognised that additional work was required in this area, and as a result, an extensive programme of research work was initiated in this area.

This included a review of the literature pertinent to the general area of uncertainty analysis, especially when informed opinion and expert judgement are being elicited. Key publications in the field of experimental psychology were identified and reviewed,

because researchers such as Slovic, Kahnemann, Tversky and others in this field had demonstrated, in peer reviewed research publications, that the elicitation of informed opinion and expert judgement could be heavily influenced by factors known as human heuristics (89, 92-94, 126).

Also, and in parallel with the above review work, a review was initiated into all of the learnings made to date (and subsequently also) from the testing that had been performed on this Quality Risk Management methodology. This was so that any learnings into how problems of uncertainty and subjectivity were encountered could be identified and acted upon. In Chapter 5 of this thesis, the results of the above review work are presented.

Final remarks in relation to the above testing activities and results:

Despite the faults that were identified with the Quality Risk Management methodology during this testing phase, there were many positives aspects identified in relation to the methodology during the above testing and evaluation activities.

For example, there was generally high level of industry interest observed in the methodology when it was presented at the GMP conference in July 2005. This was demonstrated in part by the positive comments received by the author from the UK Parenteral Society following the conference, and the fact that the Society invited the author to present the methodology at its annual meeting later in the year, in the UK.

In addition, several company representatives present at the conference advised the author that they had been seeking out a Quality Risk Management methodology that was designed to specifically address the aforementioned risk-based requirements of Annex 15 to the EU GMP Guide (6), and they stated that the nature and design of this methodology met their requirements.

In this regard, a representative of one pharmaceutical manufacturing company located, in Ireland, stated that that company had already started using Version 1 of the methodology (following its presentation by the author in October 2004 at the IMB Inspectorate Information Day), and that the methodology had yielded excellent and

value-adding results when it had been used to help determine, on a risk basis, the scope and extent of validation, and the likely impact of changes.

Following the GMP conference, the author held a conference call with two staff members of that company, and the company stated that they had applied the Quality Risk Management methodology to a variety of different manufacturing processes, and that they had completed five comprehensive Quality Risk Management exercises to date with the methodology.

In addition, the company personnel stated also that the company was planning on applying the methodology to several other areas and activities, including the water purification system on site, their general equipment qualification programme, their vial washing process, their depyrogenation tunnel, and their autoclave sterilisation process. This was a strong indication of the usefulness of the methodology across the broad GMP environment.

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Chapter 4

Generation, testing and evaluation of Version 3 of the Quality Risk Management Methodology

4.1 Introduction & Generation of Version 3 of the Quality Risk Management methodology

All of the learnings identified during the testing and evaluation of Version 2 of the Quality Risk Management methodology were compiled and evaluated, and a number of design and process modifications were made to the methodology. Version 3 of the methodology resulted from the changes that were made.

The main modifications to the methodology were the following:

- The **Quality Risk Management process** used by the methodology was modified to correct the faults that had been identified with the process during the testing of Version 2 of the methodology, as discussed in Chapter 3 of this thesis. In addition, the process was shortened, from thirteen steps to ten, and some of the terminology used by the process was changed. The changes made in this regard are discussed in detail in Section 4.1.1 below.

- The **Quality Risk Management Worksheet** component of the methodology was completely redesigned to directly reflect the ten steps of the modified Quality Risk Management process. At the same time, the Worksheet was made shorter and more instructional, and additional guidance was incorporated into the worksheet to facilitate use of the methodology. Other worksheet modifications were also made. These changes are discussed in detail in Section 4.1.2 below.

In addition, two major documentation components were added to the methodology following the testing performed on Version 2 of the methodology. One was a component known as the *Laminated Card* (as shown in Table 4.1, below). The other was a detailed guidance document on the methodology. This was structured in the form of a presentation, and provided practical guidance in relation to each of the ten steps of the new Quality Risk Management process. The guidance presentation also provided answers to some common questions which had arisen during the workshops and the other testing activities run on the methodology. The new Laminated Card component is discussed in detail in Section 4.1.2, below, and the new guidance materials developed

on the methodology are discussed in detail in Chapter 6 of the methodology, which describes all of the components making up the methodology.

4.1.1 Modifications to the Quality Risk Management Process & to its related Terminology

- Process Modifications:

The process used by the Quality Risk Management methodology was modified in several important ways as a result of the learnings gained from the evaluation of Version 2 of the methodology. Firstly, the process was redesigned from one which contained thirteen sections (or stages), to one with ten discrete process steps.

An outline of the new ten step Quality Risk Management process is presented and discussed below:

Step 1: Document Specific Information on the Quality Risk Management Exercise being undertaken:

- Identify whether the exercise is a Prospective, Retrospective or a Change Control Quality Risk Management exercise.
- Define the Item under Study & the scope of the exercise. If possible, define a boundary for the Item under Study.
- Provide relevant background information so that the reason for the Risk Management exercise is made clear.
- State any pertinent assumptions being made, especially those relating to Qualifieation & Validation, and document any significant uncertainties associated with the data being used in the exercise.

Step 2: Who's Who? - Define the Quality Risk Management Team:

- Identify the Quality Risk Management team leader, and other team members.
- The team should be multi-disciplinary, and include persons knowledgeable in the item under study.
- At least one person should have a firm understanding of the Quality Risk Management process, principles and methodology.
- If possible, there should be personnel on the team who have the necessary authority (or the means) to make key decisions regarding the implementation and funding of risk mitigation controls.

Step 3: Review the Default Definitions provided for Negative Event Probability, Severity and Detection:

- Review the default Probability, Severity and Detection definitions provided in this Risk Management Tool. These are presented on a *Laminated Card,* which accompanies the tool worksheet.
- The team then decides whether the default definitions as provided are appropriate for the specific Risk Management exercise at hand.
- This is where new or modified Probability, Severity and Detection definitions can be drawn up, if required. For example, the definitions for Probability of Occurrence can be made quantitative, or the Severity definitions can be altered to better reflect the concerns of any specific stakeholders.
- A Risk Table (or matrix) is used by this Risk Management tool, and this is also shown on the Laminated Card.

Step 4: What might go wrong? - Identify Potential Negative Events:

- Review relevant documentation, records & data, and use brainstorming techniques to identify potential Negative Events for the Item under Study. (Note: Guidance on brainstorming is provided in a Guidance document which is provided with the tool.)
- Of the potential Negative Events identified, review each, discussing their potential severities, and select and list those considered to be the most critical and/or complex Negative Events, for formal evaluation in this exercise.
- As this is a formal and rigorous Quality Risk Management methodology, only the highest priority/most important potential Negative Events should normally be selected for formal evaluation. However, any number can be selected.

Step 5: Risk Evaluation – Is the risk Acceptable, Unacceptable or Intolerable?

- For each potential Negative Event, identify and document the potential negative consequences.
- Document and critically evaluate any currently in place back-up or redundancy controls for the potential Negative Event, and assign a Severity rating.
- Identify and document the cause(s) of each potential Negative Event.
- Document and critically evaluate any currently in place preventative controls for each cause, and assign a Probability of Occurrence rating to each cause.
- Using the Risk Table provided on the Laminated Card which accompanies the tool worksheet, estimate each risk associated with the potential Negative Event.
- This results in the classification of each risk as either Acceptable, Unacceptable or Intolerable.
- Risks deemed to be Acceptable progress directly to Step 8 of the worksheet; all other risks progress to Step 6.

Step 6: Risk Evaluation – Is the Risk Adequately Controlled?

- Document and critically evaluate any currently in place detection controls for each Unacceptable & Intolerable risk.

- Assign a Detection rating to these controls, and determine whether these controls give assurance that the risk is adequately controlled and that no further controls are required.
- Risks that are considered adequately controlled progress directly to Step 8. All other risks progress to Step 7.

Step 7: Risk Control:

- Identify and critically evaluate any new or improved back-up or redundancy controls which may be put in place for Unacceptable & Intolerable risks.
- With these controls in mind, assign a new Severity rating to the potential Negative Event.
- Identify and critically evaluate any new or improved preventative controls which may be put in place for the cause(s) of each Unacceptable & Intolerable risk.
- With these controls in mind, assign a new Probability of Occurrence rating to eaeh cause.
- Using the Risk Table provided on the Laminated Card which aecompanies the tool worksheet, re-estimate each risk.
- This results in the re-classifieation of each risk as either Acceptable, Unaceeptable or Intolerable.
- Risks deemed to be Acceptable progress to Step 8 of the worksheet; all other risks continue through Step 7.
- Identify and critically evaluate any new or improved detection controls for each Unacceptable & Intolerable risk.
- Assign a Detection rating to these controls, and determine whether these controls give assurance that the risk is now adequately controlled & that no further controls are required.
- Risks that are considered adequately controlled progress to Step 8.
- For risks which are still not considered adequately controlled, Step 7 *(Risk Control),* should be repeated. (A re-design of the item under study may be necessary in order to eliininate the potential negative event.)

Step 8: Qualification and Validation:

- For each control listed on Worksheets No. 5, 6 and 7, identify the items (such as documentation, equipment, facilities, personnel resources, etc.), which are required for the control to be in place.
- Determine Critical Process Parameters, their limits, and any other acceptance criteria or required outcomes for each control.
- Determine any training and assessment of training requirements for each control.
- Determine any Qualification or Validation activities required for each control, and assign a Qualification and Validation status to each.

Step 9: Action Items:

- Document any action items arising out of the Quality Risk Management exercise, and assign responsibilities for each.
- These could be actions required to implement a control, or they could be Qualification or Validation exercises.

Step 10: Risk Communication & Continuous Improvement (Periodic Review) Activities:

- Identify and document any communication activities required for the risks identified during the exercise.
- Assign responsibilities and timelines for each communication.
- Define when the Quality Risk Management exercise should be reviewed as part of continuous improvement, and document any key areas or issues (such as the Qualification or Validation status of the item under study) to be reviewed at that time.
- Close out the Quality Risk Management exercise.

The above modified Quality Risk Management process addressed the faults that were identified during the testing and evaluation of Version 2 of the Quality Risk Management methodology, as discussed in Chapter 3.

In this regard, the requirement to critically evaluate all relevant GMP controls prior to assigning any Severity, Probability of Occurrence or Detection ratings to a potential negative event was now clearly reflected in the modified Quality Risk Management process, via the design of process steps 5 through 7.

Also, the revised Quality Risk Management process now formally required an assessment of the qualification or validation status of the Item under study during the Continuous Improvement/Periodic Review activities carried out at step 10 of the modified process. This was formally documented in a guidance presentation that was developed for users of the methodology, as discussed above.

The revised Quality Risk Management process also now more clearly and explicitly conveyed the indenture level in the Item under study at which the methodology was to be applied. No longer were up to ten potential failure modes to be identified for the Item under study, and there was now formal guidance provided on approximately how many potential failure modes (now known as potential negative events – see below) should be identified. This change was in recognition of the guidance provided in ICH Q9, which stated that "the degree of rigor and formality… can be commensurate with the complexity and/or criticality of the issue to be addressed" and that "the level of effort, formality & documentation of the Quality Risk Management process should be commensurate with the level of risk ….. (9)"

In recognition of the formal and rigorous nature of this Quality Risk Management methodology, complexity & criticality considerations were now made central to the use of the methodology. Thus, the Quality Risk Management process now more clearly showed that the use of this methodology was intended to be commensurate with the complexity and/or criticality of the item under study or the issue to be addressed. For example, Step 4 of the process now required only the highest priority/most important potential Negative Events to be selected for formal evaluation through the remaining steps of the process.

It was also now formally recognised that this methodology was not designed for use in all situations, nor to address all risk areas or concerns. In many instances, in line with ICH Q9 principles, a more informal approach to Quality Risk Management may be more appropriate, and indeed proportionate.

The revised ten-step Quality Risk Management process directly complemented and built upon some of the points made in ISPE's White Paper of 2005 (37). While focussed only on equipment and facility qualification, the ISPE paper made a number of useful recommendations on ways to achieve true risk-based qualification in pharmaceutical applications. One was that risk assessments, process development activities and experimental design work should be used to identify critical features, functions and critical process parameters, and that qualification efforts should be process-based, and focussed on the concept of risk-mitigation for patients. Steps 4 through 8 of the above modified Quality Risk Management process were designed to give explicit effect to the above thinking, and they offer a practical means for how this might be achieved.

Terminology Modifications:

As is evident from the above Quality Risk Management process, there was no longer any mention of *potential failure modes* or *severity controls* in the Quality Risk Management process. These terms were deliberately removed from the methodology when Version 3 was being developed.

As noted in Chapters 2 and 3, the use of the term 'Severity Control' had continuously proved to be problematic and difficult for users to understand, despite the clarifying text incorporated into the tool worksheet at Version 2 of the methodology. In Version 3 of the methodology, the term 'Severity Control' was replaced with the term "back-up or redundancy controls", which proved to be much more explanatory and easier to understand.

The second major terminology change was the replacement of the FMEA-based term "Potential Failure Mode" by the term "Potential Negative Event", which was defined by the methodology simply as "what can go wrong", a phrase borrowed from ICH Q9 (9). The term 'Potential Negative Event' was found to be easy to understand, applicable to a wide range of activities and areas, and perhaps more intuitive to grasp than the more commonly used terms 'Potential Failure Mode' and 'Hazard'.

A potential negative event can be a single event, or a number of individual occurrences leading to a negative outcome. In the modified Quality Risk Management process, risks arising from potential negative events are estimated, assessed and controlled via Steps 5-7 of the process. Recognising the fact that individual potential negative events may sometimes have multiple causes with different Probabilities of Occurrence, Step 5 of the Quality Risk Management process was designed to address the multiple risks that might be associated with a single potential negative event.

4.1.2 Quality Risk Management Worksheet Modifications

With respect to the changes made to the Worksheet used by this methodology, the worksheet was redesigned to directly reflect (and to give effect to) each of the ten steps of the modified Quality Risk Management process outlined above. (The modified Worksheet is presented in Appendix 1 of this Volume of the thesis.)

Additional explanatory text and a number of new elements were also incorporated into the design of modified Worksheet, to give better instruction in relation to certain activities, or to give guidance on what was required during a particular process step. For example, the new version of the Worksheet now provided clear guidance on what types of Potential Negative Events should be identified in Step 4 of the Quality Risk

Management process, and on approximately how many such Potential Negative Events should be formally processed through the methodology.
In relation to Quality Risk Management exercises that were dedicated to addressing a specific issue or problem which had been identified with the Item under study, the revised Worksheet was now clear in what should be documented in the section on Potential Negative Events.

It will be noted when reviewing the revised Worksheet that it was significantly shorter than its predecessor, with a greatly reduced number of pages (at ten), as opposed to twenty one pages in the earlier version of the Worksheet. In this regard, all of the *Notes* pages were removed from the Worksheet, as these had been found to be of little value and were seldom used. In addition, the sections of the Worksheet that contained the Risk Table and the default Probability of Occurrence, Severity and Detection levels used by the methodology were removed from the Worksheet and a new *Laminated Card* component was developed, containing these items.

The reason for the removal of the Risk Table and the default Probability of Occurrence, Severity and Detection levels from the Worksheet was because the inclusion of these elements was found to render the Worksheet (and the methodology in general) quite cumbersome to use. This was because users had to constantly go back and forth (between the pages containing those elements and the Risk Assessment-related pages of the Worksheet that were being worked on at any one time) for guidance.

The development of the Laminated Card was the result of the above changes. This was a one page, laminated document that provided the various Probability of Occurrence, Severity and Detection levels used by the methodology, as well as the Risk Table used during the Risk Assessment stage of the revised Quality Risk Management process. The structure and content of the Laminated Card are shown in Table 4.1 below.

Laminated Card for the Quality Risk Management Methodology

This Card shows the default Probability, Severity & Detection definitions for the QRM methodology. It also shows the Risk Table, with the risk acceptability criteria.

Risk = P x S

Important: The definitions shown for each P, S & D Level are default definitions; they can be modified as required. See Step 3 of the Worksheet for details.

P Probability of Occurreuce Levels for the Pot. Negative Event	
High	The Pot. Neg. Event is Likely to Occur
Medium	The Pot. Neg. Event May Occur
Low	The Pot. Neg. Event is Unlikely to Occur
Remote	The Pot. Neg. Event is Very Unlikely to Occur, or is Extremely Unlikely to occur

S Severity Levels for the Effects of the Pot. Negative Event	
Critical	The Effects are Severe - Very Significant GMP/MA Non-Compliance - Potential Patient Injury
Moderate	The Effects are Moderately Severe - Significant GMP/MA Non-Compliance - Potential Patient Impact
Minor	The Effects are Not Severe - Minor GMP/MA Non-Compliance - No Patient Impact

Risk = P x S

Pot. Negative Event Prob:	***Minor Severity***	***Moderate Severity***	***Critical Severity***
High	Unacceptable Risk	Unacceptable Risk	Unacceptable Risk
Medium	Acceptable Risk	Unacceptable Risk	Unacceptable Risk
Low	Acceptable Risk	Acceptable Risk	Unacceptable Risk
Remote	Acceptable Risk	Acceptable Risk	Acceptable Risk*

* Formal justification must be provided here

Risk Definitions:

Intolerable:
Work to eliminate the Pot. Negative Event, or build in systems or controls to ensure the effects of the Pot. Negative Event are not realised (e.g. via back-up or redundant controls).

Unacceptable:
Reduce the risk, or control the risk to an acceptable level.

Acceptable - The risk is acceptable as is. No risk reduction or new controls are required.

D **Detection Control Ratings:**

- **High** – the control will likely detect the Pot. Negative Event or its effects
- **Medium** - the control may detect the Pot. Negative Event or its effects
- **Low** – it is not likely that the control will detect the Pot. Negative Event or its effects
- **Zero** – no detection controls are in place

4.2 Research Methods & Key Research Question for the Testing and Evaluation of Version 3 of the Methodology

Following the development of Version 3 of the methodology, testing and evaluation activities were initiated. The research methods used in this regard, and the key research questions to be addressed during this testing and evaluation phase, are discussed below.

4.2.1 Challenging the Methodology with a series of GMP-related Case Studies

Several new GMP-related case studies were developed and processed through the Quality Risk Management methodology. This was in order to challenge the design and structure of the revised methodology across a broad range of GMP-related areas and activities, involving specific problems and potential risks.

The areas chosen for the new Case Studies related to:

- Product distribution and recall activities at a manufacturer of medicinal products *(Case Study 5)*
- Analytical testing activities at an Active Pharmaceutical Ingredient (API) manufacturing site *(Case Study 6)*
- The assessment of Quality Defect reports on Medicinal Products by an EU Competent Authority *(Case Study 7)*
- The final mixing & filling steps of a paracetamol oral suspension manufacturing process at a manufacturer of medicinal products *(Case Study 8)*

The above Case Studies were also designed to facilitate an evaluation of how applicable the methodology was to a range of different areas and activities within the GMP environment, and to identify any faults in the methodology that needed to be corrected. It is important to note that, for the purposes of this research and thesis, specific details of the problem areas and concerns in question for each Case Study were altered so as to not divulge the identity of the product or the company involved, and to more comprehensively challenge the practical application of this methodology.

The following is an outline of each of the four new Case Studies. (As these are the fifth through eight Case Studies presented in this thesis, they are numbered Case Studies 5 through 8.)

The first three Case Studies (5 through 7) were designed to evaluate how the methodology dealt with a number of different GMP areas not previously reviewed with the methodology - QC laboratory testing activities, product distribution and recall activities, and quality defect investigation & recall management activities.

4.2.1.1 Case Study 5:

This Case Study involved the application of Version 3 of this Quality Risk Management methodology to a product distribution and recall system at a finished medicinal product manufacturer. The company in question was a manufacturer which distributed its own medicinal products to retail pharmacies & hospitals in Ireland.

A recent recall action in Ireland had prompted the company to re-examine its arrangements for the distribution and recall of its products, and this was the basis for this particular Case Study.

The Case Study demonstrated that additional control measures were required in order to ensure batch traceability in the event of a product recall. It also demonstrated that additional Qualification and Validation activities were required in order to address the risks that were identified. This Case Study is presented in Volume 2, Part II, of this thesis, as a component of the aforementioned *Training & User's Manual* that has been developed on this methodology.

Case Study 5, together with Version 3 of the Quality Risk Management methodology on which the Case Study was based, was presented by the author at an international GMP conference in 2005. This was the UK's Parenteral Society Annual GMP conference which took place in Birmingham, UK, on November 8th, 2005. The author's presentation at this conference was the result of an invitation to the author from the Parenteral Society to present, on behalf of the Irish Medicines Board, on the general area of Quality Risk Management in pharmaceutical manufacturing.

During the conference, Version 3 of the Quality Risk Management methodology was described in detail by the author. This was followed by working through the above Case Study (No. 5) with the participants of the conference, in order to demonstrate the practical application of the methodology within the GMP environment. (Note that a number of the conference participants had already seen Version 2 of the methodology, via their attendance at the Parenteral Society GMP conference held in Cork in July of 2005, as described in Chapter 3.) An open discussion on the methodology and on the Case Study took place following the presentation. Speaking at this conference allowed the author to present Version 3 of the methodology to a cross section of the Irish and UK pharmaceutical manufacturing industry, and to obtain feedback, from an industry perspective, on the methodology. The conference was attended by technical staff members of over 15 pharmaceutical companies located within the EU, as well as personnel from several other competent authorities.

During the author's presentation, a detailed overview of the methodology was given, which described the fundamental principles behind the methodology, as well as its key features and the ten step Quality Risk Management process. The most recent version of the tool Worksheet and the new Laminated Card were also presented.

The results obtained from presentation of the Quality Risk Management methodology and Case Study 5 at this GMP conference are presented and discussed in the Results & Discussion part of this Chapter, in Section 4.3 below.

4.2.1.2 Case Study 6:

This Case Study involved the application of Version 3 of this Quality Risk Management methodology to a proposed Change Control at an Active Pharmaceutical Ingredient (API) manufacturer.

The Change Control related to a proposal to introduce Inductively Coupled Plasma – Mass Spectroscopy (ICP-MS) analytical methodology into the Quality Control laboratory at the manufacturer. ICP-MS would be applied to the QC release testing on two APIs materials, and also to the analysis of water samples at the site.

The Case Study resulted in risks being identified that had not been previously considered during the initial assessment of the particular Change Control proposal. As a result, several new GMP control measures and additional Qualification and Validation work were identified as being required. This Case Study is presented in Volume 2, Part II, of this thesis, as a component of the aforementioned *Training & User's Manual* that has been developed on this methodology.

4.2.1.3 Case Study 7:

This Case Study involved the application of Version 3 of this Quality Risk Management methodology to a non-GMP regulated activity, but one which was directly related to GMP-regulated activities. This was a Quality Defect-related market compliance programme at an EU Competent Authority for medicinal products.

In this programme, suspected Quality Defect reports are investigated by the Competent Authority (the Irish Medicines Board in this case), and the Quality Risk Management methodology was applied in order to identify any weaknesses or gaps in current procedures when investigating and handling reports of suspected Quality Defects.

The IMB's Quality Defect investigation programme was selected because it represented an area that related directly to GMP activities, but which was Competent Authority-based. This was in recognition of the fact that the guidance of ICH Q9 was intended not only for the pharmaceutical industry, but also for regulatory authorities (9). One of the aims of this Case Study was to investigate whether the Quality Risk Management methodology might help identify areas within IMB's core business activities which might benefit from risk-based qualification, validation & change control activities. This was found to be the case.

One might ask what does risk-based qualification, validation & change control have to do with the work of regulatory authorities? Are these activities not specific to GMP-regulated environments, i.e. industry? At a fundamental level, this researcher believes that qualification, validation & change control are broad, useful concepts, and that there is no reason why these concepts cannot benefit regulators as well as industry.

This is particularly so within Regulatory Compliance environments, which are concerned (directly and sometimes indirectly) with GMP, such as Inspectorates and Official Medicines Control Laboratories (127). Indeed, the Compilation of Community Procedures on Inspections and Exchange of Information, which is published by the EMEA on behalf of the European Commission, outlines certain change control and validation requirements for EU GMP Inspectorates (128). Thus, the concepts of change control and validation are already applicable to the work of GMP Inspectorates, and the Quality Risk Management methodology outlined here is designed to demonstrate how such activities can be made risk-based.

The Case Study demonstrated that additional control measures were required over those that were already in place when investigating and handling reports of suspected Quality Defects in medicinal products. It also demonstrated that certain Qualification and Validation activities were required in order to address the risks that were identified. This Case Study is presented in Volume 2, Part II, of this thesis, as a component of the aforementioned *Training & User's Manual* that has been developed on this methodology.

4.2.1.4 Case Study 8:

The last Case Study in this series was developed in order to investigate how Version 3 of the methodology compared, in terms of the results produced by it, with Version 1 of the methodology, when applied to a manufacturing process that had been previously studied with Version 1 of the methodology.

This was the paracetamol oral suspension manufacturing process that had been studied in Case Study I, in which the final mixing and filling steps in the manufacturing process were studied using the methodology. Thus, Case Study 8 involved the *re-application* of the Quality Risk Management methodology to the concerned mixing and filling process at the same finished product manufacturer.

The purpose of repeating this Case Study with the revised version of the Quality Risk Management methodology was to investigate how the modifications made to the

methodology since the first version had been developed affected the results that had been generated by that first version of this methodology. This Case Study is presented in Volume 2, Part II, of this thesis, as a component of the aforementioned *Training & User's Manual* that has been developed on this methodology. The two Case Studies (1 and 8) represented the retrospective application of two different versions of the Quality Risk Management methodology to the same Item under study.

The first version of the Quality Risk Management methodology, Version 1, that had been used during Case Study No. 1 represented a somewhat basic version of the methodology, and an early version of the Worksheet which accompanied the methodology. There was a lack of detailed guidance provided with Version 1 of the methodology in terms of the individual steps making up the Quality Risk Management process. In contrast, Version 3 of the methodology, which was used in Case Study 8, represented a more developed and detailed version of the methodology. It incorporated a more highly structured and instructional tool Worksheet, and a Laminated Card designed to facilitate steps 3, 5, 6 and 7 of the Quality Risk Management process. In addition, Version 3 was supported by detailed and practical guidance in relation to the use of the methodology in GMP environments. This guidance had been designed to facilitate the practical application of this Quality Risk Management methodology, and it had not been available at the time of Case Study 1.

As a control between the two Case Studies, the fundamental principles upon which each version of the Quality Risk Management methodology were based, and the main steps in the Quality Risk Management process which was used by each version of the methodology, had not been changed when the two Case Studies were being developed with Versions 1 and 3 of the methodology.

The above two Case Studies (1 & 8) demonstrated that, despite the differences between Versions 1 and 3 of the Quality Risk Management methodology, the results obtained from both versions of the methodology were the same in terms of the risks identified for the Item under Study, the control measures which were documented for the mitigation of those risks, and the qualification and validation requirements which were identified for the item under study.

4.2.2 Testing the Methodology in a series of practical GMP-related Workshops

A series of practical workshops were run with key stakeholder groups using Version 3 of the methodology. The stakeholders were:

- A specialist validation group from the Irish pharmaceutical manufacturing sector;
- A group of 29 GMP Inspectors from 20 countries across the PIC/S region;
- A staff member from the Market Compliance Section of the Inspectorate Department at the Irish Medicines Board.

During each of the three workshops, Version 3 of the Quality Risk Management methodology was presented to the workshop participants. This involved giving a detailed introductory presentation on the methodology, and reviewing with the participants the Quality Risk Management Worksheet, the Laminated Card and the guidance material on the methodology.

This overview described the fundamental principles behind the methodology, its key features and the ten step Quality Risk Management process used by the methodology. A hands-on and practical approach was adopted during the three workshops, and the time available to run the workshops was four hours. In addition, the first of the aforementioned GMP-related case studies was presented and worked on during each workshop.

This was Case Study 6, which related to a proposed Change Control at an Active Pharmaceutical Ingredient (API) manufacturer to introduce Inductively Coupled Plasma – Mass Spectroscopy (ICP-MS) analytical methodology to the QC release testing on two APIs and water samples at the site. This Case Study was selected because it was the most technically complex of all the Case Studies developed to date, and it was appropriate given the highly technical background of the participants of the three workshops.

Feedback obtained from the workshop participants on the methodology, and any comments made by the workshop participants on any aspect of the methodology and the

Case Study were noted, and these were used to identify any required improvements to the methodology.

4.2.3 Key Research Questions to be addressed

Three key research questions were developed in order to help structure the above testing and evaluation activities for Version 3 of the Quality Risk Management methodology.

These focussed mainly on testing and evaluating the new ten step process used by the methodology, the way detection issues were dealt with by the methodology, and the design and structure of the primary components making up the methodology, those being the tool worksheet, the new laminated card, and the supporting guidance documentation accompanying the methodology.

The key research questions were as follows:

1. Are there any faults with the way in which Risk Detection is dealt with by the methodology, or with any of the other key features and principles underlying the methodology? (With respect to detection, are there any faults from a GMP perspective with the placement of the evaluation of detection controls in Steps 6 and 7 of the Quality Risk Management process, after the risk assessment activity, at Step 6?)

2. Are there any faults with any aspect of the new ten step Quality Risk Management process used by this methodology? (Note: the ten step process was that set out in the main introductory presentation on the methodology, and as elucidated in the Tool Worksheet & Laminated Card).

3. Are there any faults with the design and structure of the modified Worksheet and the new Laminated Card, or with the guidance documentation provided with the Quality Risk Management methodology, which might prevent this methodology from being a documented, science-based, practical, systematic, transparent, flexible, and ready-made solution to facilitate compliance with the EU GMP risk-based Qualification, Validation and Change Control requirements?

4.3 Results & Discussion

Before presenting and discussing the specific results obtained in relation to each of the above Key Research Questions, the following *general results* were obtained from the various testing activities performed on Version 3 of the Quality Risk Management methodology.

4.3.1 General Results from the four practical Case Studies

The specific GMP-related Case Studies that were developed in order to challenge the design and structure of the methodology are described above in Section 4.2.1.

In relation to Case Study 5:

The results obtained from *Case Study 5* demonstrated that additional control measures were required (over the controls that were already in place) in order to ensure batch traceability in the event of a product recall. The results obtained also demonstrated that additional Qualification and Validation activities were required for the batch traceability system in order to address the risks that were identified during the Case Study.

Case Study 5 was the Case Study which had been presented at the International GMP conference held in the UK during late 2005. A number of useful learnings were made in relation to the Quality Risk Management methodology from the comments made by the attendees of the conference. While many of the comments were of a positive nature, several comments indicated that the methodology could be improved upon in several ways. For the purposes of making improvements to the methodology as a result of the learnings gained from the conference, the points made in this regard during the conference were classified by the author as *Faults* in the methodology. These Faults are discussed in detail in the Results & Discussion section below.

Improvements were made to the methodology to correct each of the faults identified at the GMP conference, and these are presented and discussed in Chapter 6 of this thesis. Chapter 6 is titled 'Generation, testing and evaluation of the final Version of the Quality Risk Management Methodology.'

Despite the faults that were identified with the Quality Risk Management methodology as a result of the Case Study work, a generally high level of industry interest in the methodology was observed at the GMP conference. For example, several company representatives and pharmaceutical consultants present at the conference expressed an interest in using the methodology, and one consultancy company has since confirmed that they refer to the methodology during their Quality Risk Management training activities. Also, one attendee from a major multinational company stated that this approach would work very well with that company's current thinking on the application of Quality Risk Management to microbial contamination issues. In addition, the editor and publisher of the UK journal GMP Review, who were in attendance at the GMP conference, requested the author to write a scientific article on the methodology for readers of the journal.

A high level of support was expressed at the GMP conference in relation to the qualitative, yet rigorous and formal nature of this methodology, particularly with respect to how the methodology focussed specifically on GMP controls, and how it required a critical evaluation of current and proposed controls with respect to how they mitigated risk.

In relation to Case Study 6:

Case Study 6 resulted in risks being identified in relation to the ICP-MS analytical instrumentation that had not been previously considered during the initial assessment of the particular Change Control proposal.

As a result, several new GMP control measures and additional Qualification and Validation work were identified as being required.

In relation to Case Study 7:

The results obtained from *Case Study 7* demonstrated that additional control measures were required (over those that were already in place) when investigating and handling reports of suspected Quality Defects in medicinal products.

It also demonstrated that certain Qualification and Validation activities were required at the Competent Authority in order to address the risks that were identified in relation to the current Quality Defect investigation procedures.

In relation to Case Study 8:

The results obtained from *Case Study 8*, which involved the re-application of this Quality Risk Management methodology to the paracetamol oral suspension manufacturing process that had been previously studied via Case Study 1, demonstrated that, despite the differences between Versions 1 and 3 of the Quality Risk Management methodology, the results obtained from both versions of the methodology were the same in terms of the risks identified for the item under study, the control measures which were documented for the mitigation of those risks, and the qualification and validation requirements which were identified for the Item under study.

4.3.2 General Results from the series of practical Workshops

The aforementioned series of practical workshops represented the main (and probably the most important) testing activity carried out on any version of the methodology up to that time.

The first workshop was held with members from the Irish pharmaceutical manufacturing industry, and it was attended by 29 staff working either in validation or quality-related roles at 21 pharmaceutical manufacturing companies located in Ireland. These staff made up the Validation Sub-Group of *PharmaChemical Ireland*. PharmaChemical Ireland is an industry representative body in Ireland representing pharmaceutical manufacturing companies, and it meets regularly with the Irish Medicines Board to discuss various GMP and related inspection issues. The Validation Sub-group was a working group within PharmaChemical Ireland, which was concerned with qualification and validation activities. The workshop was held in Cork in November 2005, and was hosted by PharmaChemical Ireland.

The second workshop was run in Dublin, Ireland, in November 2005, with a staff member from the Irish Medicines Board. This person was working in the Market

Compliance Section of the Inspectorate Department, and had expertise in analytical chemistry and microbiology.

The third workshop, held in Düsseldorf, Germany during June 2006, was run with 29 GMP inspectors from 20 countries, all of which were members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S). The countries represented were as follows: Germany, Norway, Hungary, Spain, Singapore, Denmark, USA, Malta, Greece, Australia, Czech Republic, Slovak Republic, The Netherlands, Switzerland, Austria, Italy, Lithuania, Cyprus, UK and Japan. This workshop was hosted by PIC/S, an organisation made up of GMP Inspectorates from various countries, whose purpose is to facilitate Inspector training and to promote compliance with GMP.

The above three workshops were designed to be identical in how they were run. This meant that the same version of the Quality Risk Management methodology was presented to the workshop participants at each workshop, and this included presenting the same worksheet, laminated card and guidance material on the methodology. In addition, the same practical, GMP-related case study was presented and worked on during each workshop. The Case Study used during the workshops for working through the methodology was that involving the proposed Change Control at an API manufacturer to introduce ICP-MS analytical methodology to the QC release testing on two APIs and water samples at the site (Case Study 6). This Case Study was selected because it was the most technically complex of all the Case Studies developed to that date, and it was appropriate given the highly technical background of the participants of the three workshops.

At the start of each workshop, the author stated that the workshop was intended to be a mutual learning exercise for the author and the participants, aimed at identifying whether there were any technical or conceptual difficulties, or faults, with any aspect of the methodology. The workshops were designed to be informal and interactive between the author and the participants. Audio-visual presentations, together with the worksheet, the laminated card and the completed case study, were used as the means of presenting the fundamental principles underlying the methodology, its key features, and the overall structure of the tool. A critical evaluation of, and discussion on, these

materials was encouraged by the author, and plenty of time was set aside for questioning and discussion on all that was presented.

When introducing the attendees of the workshops to the methodology, the key features of the methodology were described. Some of these key features were as follows:

- *This methodology represents a formal, documented and rigorous approach to Quality Risk Management specifically designed for GMP environments. Its use is designed to be commensurate with the complexity and/or criticality of the issue or item under study to be addressed, and in this regard, the methodology has been designed around the principles and guidance presented by ICH Q9 (9).*

- *The methodology is designed to facilitate compliance with the risk-based requirements of Annex 15 of the EU GMP Guide, which concern not just risk-based Qualification and Validation, but also risk-based Change Control activities (6).*

- *The methodology follows a defined ten-step process, which utilises an instructional worksheet and laminated card, as well as a detailed guidance presentation, to guide users through each step of the process.*

- *The methodology makes uses of multi-disciplinary teams to complete the Quality Risk Management exercise, which involves identifying, assessing, controlling, communicating and reviewing the risk associated with potential negative events.*

- *The methodology makes uses of the concept of potential negative events. A potential negative event is defined simply as "what can go wrong" with the item under study. A negative event can be a single event, or a number of individual occurrences leading to a negative outcome. Risks arising from negative events are estimated, assessed and controlled in Steps 5-7 of the Quality Risk Management process. Recognising the fact that individual negative events can have multiple causes with different probabilities of occurrence, the methodology is designed to address the multiple risks which may be associated with a single negative event, as documented in Step 4 of the tool worksheet.*

- *The methodology places a high emphasis on evaluating the GMP Controls that are in place for the item under study, and in this regard, a critical evaluation of current (as well as new or improved) GMP controls is required with respect to how they mitigate or control risk.*

- *Qualification & Validation considerations are integral to use of the methodology. For example, identifying the current qualification or validation status of all GMP controls involved in risk mitigation or risk control is a central requirement of Step 8 of the process, and the qualification & validation requirements for those controls are also determined. In addition, given that some GMP controls required to address an identified risk may be personnel/training-related, the requirements for personnel competency and training-related controls are likewise evaluated and determined in Step 8 of the methodology.*

- *The concept of determining a Risk Priority Number for each risk is not used in this methodology, and Detection ratings are <u>not used</u> to estimate or prioritise the risk associated with any potential negative event.*

- *The methodology offers a large degree of flexibility in several important respects. For example, with respect to GMP controls, the methodology recognises the fact that different types of controls may be encountered in GMP environments that provide for risk mitigation or control, and it is designed to allow for these to be characterised and evaluated in an appropriate manner. (While some controls may have associated critical process parameters that can be measured or monitored, (such as an in-process acidity test, which has pH as its critical process parameter), other types of controls, (such as personnel training, or supplier qualification activities), are not so easily described in terms of critical process parameters, and the methodology makes provision for this, by not exclusively focussing on critical process parameters. The methodology addresses this difficulty through the design of Step 8 of the worksheet. Step 8 allows one to define acceptance criteria or required outcomes for a control, (such as satisfactory performance in a training assessment test), without having to determine formal critical process parameters for the control which can be measured or monitored. Either way, and regardless of the*

terminology used in Step 8 of the worksheet, the end result is the same, in that the key measurables and expected outcomes for the control in question are defined, and their qualification and validation requirements identified.

In general, substantial positive feedback in relation to the applicability, usefulness and scope of the methodology was received by the author from the participants of the three workshops. Positive feedback was also received during the workshops in relation to the key features of the methodology, and no faults or difficulties were identified in this area. Three examples are provided in this regard, as follows:

Example 1 of Positive Feedback:

At the PIC/S workshop, the GMP Inspectors commented very favourably on the design, content and structure of the Laminated Card, and many supported the feature of the methodology which allowed the default definitions for the Probability of Occurrence, Severity and Detection ratings to be customised.

Example 2 of Positive Feedback:

In relation to GMP controls and the requirement in the methodology for a critical evaluation of current and proposed controls with respect to how they mitigated risk, many attendees of the Pharmaceutical Industry workshop commented favourably on how the methodology required Step 8 of the worksheet to be completed for current controls as well as for new or improved controls.

In this regard, there was discussion about how Steps 5, 6 and 7 of the Quality Risk Management process required a critical evaluation of the merit of each current and proposed new or improved GMP control, from the perspective of risk control and protection of the patient, and the fact that this was required even when the risk was considered to be acceptable without any new or improved controls being put in place was strongly supported.

Example 3 of Positive Feedback:

Many of the Pharmaceutical Industry workshop participants commented also on the practical and pragmatic nature of certain features of the methodology. For example, the fact that the methodology formally recognised that during Quality Risk Management activities, there may be some risks identified which cannot realistically be eliminated or reduced to an acceptable level with current or new controls or resources, but which may be controlled to an acceptable level by other means, was strongly supported. (This was the basis of Principle 5 underlying the methodology, and was given effect in the design of steps 6 and 7 of the Quality Risk Management process.) There were also comments made that the methodology represented a useful and structured approach to problem solving.

Other Comments and Findings:

Many of the regulatory and industry attendees at the three workshops expressed the view that, at this early stage of the utilisation of formal Quality Risk Management methodologies within GMP environments, this particular methodology represented a highly valuable and appropriate application of the principles of ICH Q9, and a solution to addressing the risk-based qualification, validation and change control requirements of Annex 15.

Regarding the fact that Risk Priority Numbers (RPNs) were not utilised by this methodology in any way, there was much unsolicited discussion at the PIC/S workshop on the disadvantages of using RPNs during formal Quality Risk Management activities, particularly with respect to the use of detection ratings in RPN calculations, and the lack of good science behind the selection of RPN cut-off values. There was strong support for how this methodology did not use RPNs as a means of prioritising risks.

Unexpectedly, however, a high level of specific discussion occurred during the above testing phases on certain features of the methodology that were not expected to prompt much interest. This occurred during all of the testing activities performed, and many useful points were made in relation to those features. For example, the use of multi-disciplinary teams was a feature of the methodology that was the subject of much debate and discussion during each of the three workshops, particularly in relation to the

management of staff on such teams, and whether the composition of such teams had to be fixed for any one Quality Risk Management exercise, or whether people could move in and out of such teams as needs arose. Training on Quality Risk Management methodologies was also a topic of much discussion, and a number of useful learnings were made in this regard. See below for additional information in this area.

Given that one of the main features of the methodology was that it was designed to facilitate risk-based Qualification and Validation, there was discussion at the Industry workshop on whether it was likely that the use of Quality Risk Management in GMP environments will ultimately serve to reduce validation costs in manufacturing. While this area is one which is not yet well covered in the pharmaceutical literature, and while the discussion in this regard was inconclusive, a common opinion expressed was that the use of formal Quality Risk Management in GMP environments will help companies better identify where validation efforts should be targeted, and where validation resources should be spent. It was also stated that such methodologies do help to focus validation efforts to critical areas, and that it may reduce resource requirements in the long term.

Many useful comments were made during a break-out session that took place among the participants of the Industry workshop on the pros and cons associated with using Risk Management tools across company quality systems. These comments, both negative and positive, provided a useful insight into industry concerns associated with the application of formal Quality Risk Management approaches in GMP environments.

In this regard, some of the negative comments related to the level of resources, expertise, training and time required for the use of formal Quality Risk Management methodologies, the fact that "selling" of the methodology may have to be undertaken to convince others within a company and within regulatory authorities of the benefits of such approaches, the fact that it was sometimes difficult to know which tool to use and where to start, and the fact that there can be subjectivity associated with Quality Risk Management activities generally.

Concerns were also expressed in relation to performing a risk assessment exercise in one system but not in another, and how this might be justified to GMP Inspectors. It was also stated that the implementation of Quality Risk Management methodologies site-wide can be difficult for companies to achieve, as the responsibility often falls (perhaps unfairly) to validation personnel within a company, and this places a high burden on Validation staff, that is sometimes difficult to achieve.

On the positive side, there were comments that such methodologies are beneficial in that they provide a structured approach to problem solving, and are a formal and documented means for justifying proposals to Regulators and Regulatory Affairs staff. It was commented that their use may result in improved currently-in-place controls, and less duplication in work (e.g. for cases where some controls are shown via formal Quality Risk Management exercises not to be value-adding).

Others commented that such methodologies help to prioritise work actions, reduce project work, assess Change Controls, justify capital expenditures, increase process understanding, help achieve regulatory compliance, and may reduce company resource requirements in the long term. It was stated that these methodologies help to focus the validation effort to critical areas, and may lead to a reduction in validation requirements.

A comment was made that once Risk Management is in place throughout the company (as an underlining philosophy of the company), then this makes it easier to carry out Risk Management exercises. Other comments expressed the view that such methodologies can help to increase the confidence and trust of regulators in the process under study, *and provide a good forum for discussion.*

4.3.3 Results for Key Research Question No. 1

Key Question 1 was as follows:

- *Are there any faults with the way in which* ***Risk Detection*** *is dealt with by the methodology, or with any of the other key features and principles underlying the methodology? With respect to detection, are there any faults from a GMP*

perspective with the placement of the evaluation of detection controls in Steps 6 and 7 of the Quality Risk Management process, after the risk assessment activity, at Step 6?

No faults were identified during any of the testing stages with the way in which Risk Detection was dealt with by the methodology, or with ***Principle No. 9***, which states that in GMP environments, a high detectability of risk does not necessarily mean that the risk is eliminated or adequately controlled.

On the contrary, when this feature of the methodology was presented and discussed in each of the three workshops and at the Birmingham conference, strong support was expressed for this aspect of the methodology. In addition, during the PIC/S workshop with GMP Inspectors, several inspectors stated that the use of detection ratings during Quality Risk Management activities was an area that was often unscientific and subject to abuse, and that this area required careful review during GMP inspections at companies utilising Quality Risk Management methodologies.

With respect to the other eleven Principles upon which the methodology was based, strong support was generally observed for those principles, and no faults were identified with any. However, much discussion did occur on various aspects of the principles, and the following was noted.

In relation to ***Principle No. 1***, which stated that the scope and extent of qualification and validation, and the likely impact of changes, should be determined and managed on a risk basis, different views were expressed during the workshops in relation to the implications of this Principle. There were two main themes to the findings in this regard. The first concerned the general implications of Principle 1, while the second concerned Change Control issues. These findings were as follows:

There was a high level of discussion at the UK GMP Conference and also at the PIC/S workshop on the general and practical implications of Principle 1. One attendee at the that Conference disagreed strongly with the spirit of this principle, expressing an

opinion that there was generally too much emphasis on Quality Risk Management activities within GMP environments at that time. The conference attendee in question did not agree that the scope and extent of qualification and validation, or the likely impact of changes, should be determined and managed on a risk basis using formal methodologies such as this one. The same conference attendee stated that there was no need for such methodologies, as all great scientific principles were simple, and that the use of such methodologies was not required.

The above view was not supported by the author, and also, many of the other attendees of that same workshop expressed the opposite view. Several participants stated that they found the methodology to be highly relevant, useful, and applicable to GMP environments, and that the methodology represented an important solution for helping to determine the scope and extent of qualification and validation, and the likely impact of changes.

With respect to the latter part of ***Principle No. 1***, which concerned Change Control proposals and which led to the development of this methodology for Change Control activities, one workshop participant questioned the appropriateness of this principle, and the general value of this methodology in change control applications. This participant explained that Change Control programmes in companies are usually designed to address potential risks presented by a proposed change. This participant described, for example, how her company's Change Control procedure contained a number of pre-defined risk-based questions that were designed to identify potential risks introduced by the proposed change. She stated that while such Change Control procedures may not have been designed as formal Quality Risk Management methodologies, they could be viewed as providing a Quality Risk Management approach to Change Control activities.

Other workshop participants disagreed with the above opinion, particularly during the PIC/S workshop, stating that existing Change Control procedures do not usually represent formal Quality Risk Management approaches, and also, that it was important to formally separate Quality Risk Management methodologies from Change Control procedures.

The author stated that this Quality Risk Management methodology had been designed to complement existing Change Control procedures, not to replace them. It was clarified by the author that it was not intended for this methodology to be applied to all change control proposals at a manufacturing site. Instead, this methodology was designed for situations in which the complexity and/or criticality of the proposed change were such that an extra degree of rigor and formality were required in the process for identifying, managing and communicating risks associated with the proposed change, and when all of the elements of the Quality Risk Management process were required, including formal Risk Communication and Periodic Review activities.

The author agreed, however, that Change Control procedures do often provide a useful means of identifying risks associated with a proposed change, and that this is often achieved via the incorporation of risk-based questions in such procedures. However, while pre-defined risk-based questions are a valuable component in change control procedures, it was explained by the author that it is sometimes observed when inspecting company Change Control procedures that such questions are often either too general in nature, or that they represent only a narrow check-list of items for consideration when assessing risk. For example, risk-based questions in Change Control procedures often focus on identifying the impact of the proposed change on items such as product quality, training, currently documented procedures, current equipment cleaning procedures, qualification or validation status, etc. Yet, important key questions are sometimes not asked, such as 'What can go wrong if we implement this change?' or 'If this change is implemented as proposed, what risks are associated with it, and might any new risks be introduced by the controls put in place to give effect, or to control, the change in the first place?'

This latter point directly related to ***Principle No. 10*** of the methodology, which recognised how Risk Control measures may actually introduce new risks. An example here is the use of product-contact PAT-type controls that may be installed into a reactor or granulating vessel, to monitor a parameter such as pH or water content. In this regard, a number of workshop participants commented positively on how the

methodology formally addressed such issues in Step 7 of the Quality Risk Management process.

The author explained that this methodology was designed to encourage companies to take a step back from their actual Change Control process, and to objectively consider the proposed change within a formal, rigorous and dedicated Quality Risk Management approach, designed to ensure that the potential risks presented by the change are identified, managed and communicated in a comprehensive and structured manner. Indeed, the ICP-MS case study demonstrated this at a practical level, showing how the initial evaluation of the Change Control proposal had not identified some important qualification and validation activities resulting from some important, but overlooked, risks.

In relation to ***Principle No. 2***, which stated risk is the combination of the probability of occurrence of harm and the severity of that harm, and that harm is considered to be damage to health, including the damage which can occur from loss of product quality or availability, different views were expressed during the workshops in relation to the acceptability of this Principle. In this regard:

During the Industry workshop, two participants expressed an opinion suggesting that the latter part of this principle may not be valid. This related to the situation documented in the ICP-MS Case Study (No. 6), in which a potential negative event potentially impacted upon product availability, but did not impact upon product quality. It was argued that, in such cases, the issue of concern did not come within the remit of GMP control or regulation, and that it should not have been considered as a GMP issue. It was argued that such risks were solely business-related, not GMP-related, as the loss of the company's ability to test and release batches of the API products in question, as documented in the aforementioned Case Study, only impacted upon the finances of the company.

Interestingly, and in contrast to the above workshop comments, several GMP inspectors at the PIC/S workshop expressed the opposite view, and commented favourably on the

way in which the methodology dealt with product unavailability issues. They also commented favourably on how product unavailability issues were directly linked to the definition of harm as presented by ICH Q9, by the methodology via Principle No. 2.

The author explained that the risk of product unavailability as presented in the ICP-MS Case Study was GMP as well as business-related. This was because the potential negative event that led to the potential loss of product availability related to the breakdown of the analytical instrumentation, and to the improper usage of the instrumentation by laboratory analysts. While these issues clearly had a business impact, they were also clearly related to GMP activities.

In relation to ***Principle No. 11***, which stated that performing Quality Risk Management exercises can be improved through the use of multi-disciplinary teams, this is a common feature of most well established Risk Management applications. While no faults were identified with this Principle, there was considerable discussion during the workshops on how to give the principle effect at a practical level. In this regard, the discussions focussed on how best to make use of multi-disciplinary teams during Quality Risk Management exercises. For example:

- *While the importance of using multi-disciplinary teams was generally fully supported by the workshop participants (and also by the GMP conference attendees), the training of such teams was identified as an area of considerable concern, and one which had the potential to hinder the benefits of using multi-disciplinary teams. Without adequate training on the methodology being used by the team in question, many participants stated that, in their experiences, the Quality Risk Management exercises carried out by such teams were often prone to problems of disagreement and uncertainty.*

- *Various approaches to team training were discussed, and one pharmaceutical consultant present at the GMP conference described the tangible benefits to be gained from using case studies not in any way related to GMP activities when training users on a particular Quality Risk Management methodology. Using car crash scenarios to facilitate training on the Fault Tree Analysis Risk Management*

methodology, for example, or showing how Process Mapping tools may usefully be applied to common home-based activities such as cutting the grass, had been found to be of high practical value during training activities on those methodologies. (Interestingly, at the time of the GMP conference, such training work was actually an ongoing area of current interest for the author, and a non GMP-related case study for training purposes was under development at the time. This is discussed in more detail in Chapter 6.)

4.3.4 Results for Key Research Question No. 2

Key Question 2 was as follows:

- *Are there any faults with any aspect of the new ten step Quality Risk Management process used by this methodology? (Note: the ten step process was as set out in the main introductory presentation on the methodology, and as elucidated in the Worksheet & Laminated Card, and in the case studies which were presented at the workshops.*

No technical faults were identified with any aspect of the new ten step Quality Risk Management process. On the contrary, many of the workshop participants and attendees of the GMP conference stated that the process was a practical and useful approach for addressing difficult or complex problems. One participant, for example, stated that this Quality Risk Management approach would be useful in justifying reduced testing or parametric release activities, as it represented a practical means for evaluating change control proposals in this regard.

In this regard, the participant commented how this methodology was suitable for evaluating the impact of reducing the extent of testing performed on a starting material or finished product, or of introducing parametric release, etc. This was because the process behind the methodology required a formal evaluation of the GMP controls which were in place for the manufacturing process or item under study, and this allowed one to determine what controls might not be useful or which do not add value, and what new controls, if any, might be needed if some of the current controls are eliminated.

There was generally strong support expressed during all of the testing phases for the ten-step process that the methodology used. This was also manifested in the fact that, at the GMP conference, several attendees expressed an interest in using the methodology within their own companies, and the author has since learned that several companies, including one pharmaceutical consultancy company involved in providing training on Quality Risk Management methodologies, have adopted the methodology into their work activities (129).

A number of unanticipated and unusual queries were raised during the workshops in connection with using the ten step Quality Risk Management process. One such query was whether the ten step process should be suspended when a new or improved control is proposed during a Quality Risk Management exercise to address a risk, until approval is granted to implement that control.

The author responded that the process was designed to allow the exercise to proceed without putting the exercise on hold whenever a new or improved control initiative is proposed. In fact, it is preferable in this regard that the exercise is allowed to continue to completion. This is because the worksheet was designed to provide, when completed, comprehensive and documented risk-based evidence for the need for the control in question, as well as information on the items required to put the control in place.

4.3.5 Results for Key Research Question No. 3

Key Question 3 was as follows:

- *Are there any faults with the design and structure of the modified Worksheet and the new Laminated Card, or with the guidance documentation provided with the Quality Risk Management methodology, which might prevent this methodology from being a science-based, practical, systematic, flexible, and ready-made solution to facilitate compliance with the EU GMP risk-based Qualification, Validation and Change Control requirements?*

The structure and design of the Worksheet and Laminated Card were the focus of much interest and discussion during the three workshops, and also at the UK GMP conference. While no faults were identified with these components, some useful observations were made in relation to these items.

For example, in relation to the structure of the tool worksheet, a query was raised concerning the order of the various items on page 5 of the Worksheet. This was the Risk Evaluation part of the worksheet. The issue concerned whether the section on back-up systems or redundancy controls in this page of the worksheet was placed in the correct location on this page - should it not have been placed after the section in which the cause of the potential negative event was documented? This was suggested because sometimes, a back-up system or a redundancy-type control might be related to the cause of a particular negative event, and thus only after the cause is identified may such a control be identified.

The author advised that the design of the worksheet was flexible in how each section was to be completed, and that there was no need to move the location of where the back-up systems and redundancy controls were to be documented. In fact, it would be counter-productive to do so, because such controls relate primarily to the effects of the potential negative event, and it was important for these to be documented and critically evaluated before any Severity rating was assigned to the potential effects of the potential negative event. The author explained that this was why they were located in the position shown on page 5 of the worksheet.

The author acknowledged, however, that the above observation was useful and important. During the development of the Case Studies using the methodology, there were instances in which back-up systems or redundancy-type controls were identified after the cause of a potential negative event had been determined. This had proven useful, as it helped to then refine the severity ratings that were assigned to the potential effects of the potential negative event. When this occurred, the team simply went back to the section in the worksheet where the back-up systems or redundancy-type controls

were to be documented, and the control in question was documented there. If any change in the assigned Severity rating was then required, this change was made, and the methodology allows for this. (Note: this is a good example of the merit of having at least one member on the Quality Risk Management team who is very familiar with the methodology and how it is used.)

In general, there was a high level of acceptance observed for the Worksheet and Laminated Card during all of the testing stages mentioned earlier in this chapter. For example, when working through the practical ICP-MS Case Study during the workshops, many participants commented that the Worksheet and Laminated Card components were well designed, and intuitively easy to use. Several participants also commented that the tool worksheet represented a systematic and scientific means of applying the Quality Risk Management process to manufacturing processes and change controls. Here, there was considerable discussion during the workshops with regard to the way in which the methodology disallowed the assigning of probability of occurrence, severity and detection ratings to potential negative events before the GMP controls potentially influencing those ratings were documented and critically evaluated.

Several workshop participants stated that this was an example of good science, and that it was useful in terms of reducing the level of subjective guesswork that is often associated with assigning such ratings during Quality Risk Management activities.

There were also several positive comments made during the workshops in relation to how the Quality Risk Management methodology offered a high degree of flexibility. This was in terms of how the individual process steps were to be executed. The design of Step 8 (Qualification and Validation), for example, was the subject of careful examination during the workshops, and many workshop participants commented that they liked the flexibility offered by this Step, when GMP controls were being evaluated for their qualification and validation requirements. (This related to the fact that critical process parameters did not necessarily have to be identified for a particular control in order for the qualification and validation requirements for that control to be determined.)

As discussed in some detail in Chapter 2, with certain types of GMP controls, such as training and supplier approval activities, there may be no clear critical process parameters associated with them, but there still may be definite qualification and validation requirements associated with those controls which need to be addressed. The design of Step 8 of the Worksheet allows for such situations.

Another example of how the methodology was observed to offer flexibility in its approach to Quality Risk Management related to the Periodic Review element of Step 10 of the process. When discussing this element of the methodology during the workshops, some participants commented on how the methodology was not overly prescriptive in how periodic review activities were to be carried out. This related to the fact that it was left up to the team performing the Quality Risk Management exercise to define the required frequency of any such reviews to be carried out, and the aspects of the exercise that were to be reviewed. The reviews could be performed annually, or in longer or shorter intervals, and also, the methodology allowed for certain aspects of a Quality Risk Management exercise to be reviewed at a different time-point than that planned for the exercise in general. Case Study No. 5, (in Section 4.2.1.1 of this thesis) which related to the application of this methodology to the product distribution and recall system in place at a manufacturing company provided a practical example of this point. This flexibility was seen as a positive feature by those who commented on it at the workshops.

Regarding the Risk Table for the methodology that was contained on the Laminated Card, there was general support observed during the workshops and the GMP conference for the design of this Risk Table in this version of the methodology. The author specifically explained to the workshop participants and the GMP conference attendees how the Risk Table had been modified to take into account the learnings gained when using the methodology in different situations. (As discussed in Chapter 3, this change in the Risk Table related to how the risk associated with a potential negative event that had been assigned a Critical Severity and a Remote Probability of Occurrence would be rated. The Risk Table was now designed to rate such risks as being acceptable, if the appropriate justification was provided, and the author explained the background to this change.)

Detailed discussions were held during the PIC/S workshop and the GMP conference on this aspect of the Risk Table. One conference attendee did not agree with this risk rating being assigned to such potential negative events, as he felt that a potential negative event with a critical severity should never be considered to be acceptable, no matter how low the Probability of Occurrence was for the potential negative event. The author explained the reason for this aspect of the risk table, as described in Chapter 3. Generally, however, there was strong support for the design of the Risk Table during this GMP conference, and at each of the three workshops. One inspector at the PIC/S workshop cited the example of performing a media fill in an aseptic suite as a practical demonstration of this feature of the risk table. In media fills, the EU accepted contamination rate is 0.1% with a 95% confidence limit during process simulations (6); this is obviously not the same as a zero growth, and such contamination events can reasonably be characterised as having a critical severity and a remote probability of occurrence.

Notwithstanding the above positive observations, a number of faults were identified during the workshops with certain aspects of the methodology. These all related to the lack of detailed guidance available on the methodology for users.

Three areas were identified requiring more detailed guidance. These were:

- ***Fault 1***: How Step 4 of the Quality Risk Management process was to be completed;
- ***Fault 2***: How the methodology dealt with disagreements of opinion during brainstorming activities;
- ***Fault 3***: The items that might trigger the Periodic Review element of the Quality Risk Management methodology.

Each of these is discussed in turn below.

Fault 1 - How Step 4 of the Quality Risk Management process was to be completed:

With regard to the first fault identified - how Step 4 of the Quality Risk Management process was to be completed in practice - the specific workshop observations in this area centred around the way in which potential negative events identified during Step 4 were to be screened and then selected (or rejected) for formal assessment in the remaining steps of the Quality Risk Management process.

From the discussion at the Industry workshop, it was clear that too little guidance had been provided for this screening and selection activity in the Questions & Answers guidance document supplied with the methodology. Participants of this workshop were unsure how exactly this screening and selection process should be carried out, especially in cases where a relatively large number of potential negative events (perhaps ten or more) may have been documented during the brainstorming stage of Step 4.

Queries were also raised during the above workshop on how the methodology dealt with the potential negative events that were identified at Step 4 but which had not been selected for onward processing through the remaining steps of the Quality Risk Management process. Should these potential negative events just be ignored, or should it be formally documented and justified why they were not routed through the remaining steps of the process?

One attendee at the GMP conference questioned whether the design of Step 4 might limit the level of usability of the methodology for large, complex, multi-step manufacturing processes. This person stated that her company had been intending to apply a formal Quality Risk Management methodology to all of the steps in a large, complex manufacturing process, and the question was asked whether this Quality Risk Management methodology would be suitable for such applications, given that it was designed to handle a relatively small number of potential negative events.

In response to the above questions and observations, the author made the following points.

- This was a formal and rigorous Quality Risk Management methodology, utilizing a detailed Quality Risk Management process comprising of ten discrete steps, and a detailed, multi-page worksheet requiring formal completion. Given this fact, and in line with the guidance presented by ICH Q9, this particular methodology had been designed to be applied to only the most critical and/or complex parts, issues or problems associated with the item under study. In this regard, due to the rigorous and formal nature of the methodology, it was not recommended that the methodology be applied to every part of a large manufacturing process, or to address all issues that might be encountered with such a process.

- The value of this methodology was best realised when it was applied to the most difficult, critical and/or complex parts of such a process. In this regard, it was designed to allow one to formally and rigorously assess the risk associated with a relatively small number of potential negative events – those considered to be the most important. If a large number of potential negative events are to be studied, a less-detailed cause and effect approach, a HACCP approach, or an FMEA-based approach may be more appropriate. For the less important, or more minor, potential negative event issues identified with the manufacturing process in question, these may be more appropriately addressed by other, less formal, Quality Risk Management approaches.

The author also explained how the above approach was based upon the principles of ICH Q9, which stated that the "degree of rigor and formality… can be commensurate with the complexity and/or criticality of the issue to be addressed", and that it was not always appropriate, nor necessary, "to use a formal Quality Risk Management process" in all situations. ICH Q9 also states that "level of effort, formality & documentation of the Quality Risk Management process should be commensurate with the level of risk (9)"

In relation to determining at Step 4 of the Quality Risk Management process which potential negative events should be selected for onward processing through the remaining steps of the process, the author explained how the following approach had

been found to be the most useful during the development of the various case studies on the methodology:

In Step 4 of the Quality Risk Management process, following the data review and initial brainstorming activities, the team is required to discuss and review all of the potential negative events identified, in terms of their expected consequences and their likelihood of occurrence. In this regard, the strength of evidence for the likelihood of occurrence of each potential negative event should be considered, and the severity of the consequences of each potential negative event should be discussed.

The level of complexity associated with the each potential negative event, in terms of how the potential negative event might occur, should also be considered. At this stage, those potential negative events considered by the team to be the most important, in terms of their potential consequences and/or complexity, should be selected for formal onward processing in the remaining steps of the Quality Risk Management process. However, the likelihood of occurrence of each potential negative event should also be taken into account, and if it is agreed at Step 4 that a potential negative event has only a remote likelihood of occurring, then this potential negative event should not normally be selected for onward processing through the remaining steps of the process, unless there is good reason for doing so. The decisions made in relation to the above evaluations and considerations should be documented during step 4 of the process.

In relation to dealing with the potential negative events that had been identified at Step 4 but which had not been selected for onward processing through the remaining steps of the Quality Risk Management process, the author responded that there should be a record made of what these potential negative events were, and why they were not formally routed through the remaining steps of the process.

In this regard, one option was to decide to manage any potential risk associated with those potential negative events in a less formal manner than this methodology requires. Alternatively, the team may decide that these potential negative events should actually be processed through the remaining steps of this Quality Risk Management process at some later date, perhaps during the planned review of the exercise as part of Periodic Review activities, and this should be documented in Step 10 of the worksheet.

Alternatively, the team may just recommend that these potential negative events be reviewed again at the next review of the exercise, to determine whether at that time they should be formally routed through the remaining steps of the process. Again, this should be documented in Step 10 of the worksheet.

Lastly, there may be no need to give any more consideration to those potential negative events at all, following the above evaluation at Step 4 of their expected consequences and their likelihoods of occurrence. As before, the decisions made in relation to the above should be documented during step 4 of the process.

The author acknowledged that the above steps were not clearly described in the methodology, and that guidance was required in the methodology in this regard. During the discussions on the execution of Step 4 of the Quality Risk Management process, the author explained that it was important to recognise that there may be some level of subjectivity and uncertainty associated with the execution of this Step 4. This was because the identification and screening of potential negative events can be a subjective task to a degree, especially when expert judgement and personal opinions are used. (Chapter 5 provides a detailed discussion in this regard.) ICH Q9 explains how different stakeholders may have different concerns in relation to the item under study, and that they might perceive different consequences for the same negative event.

This can lead to differences of opinion on which potential negative events are the most important. Also, there may often be uncertainties associated with some parts of Quality Risk Management processes, particularly in relation to estimating the probability of occurrence of a particular potential negative event. Thus, these factors may influence what potential negative events are selected as the most important for formal onward processing in the remaining steps of the Quality Risk Management process.

Fault 2 - How the methodology dealt with disagreements of opinion during brainstorming activities:

The second fault identified with the guidance documentation during this testing phase related to the lack of detailed guidance for dealing with disagreements of opinion which might occur during brainstorming sessions.

During the elucidation of the ICP-MS Case Study, for example, there was much discussion and debate in each of the three workshops on the probability of occurrence values that were assigned to the causes of the potential negative events. Different opinions were sometimes expressed on the probability of occurrence values that should be assigned, and this was one example of how subjectivity and uncertainty can be experienced during Quality Risk Management exercises.

While some basic guidance had been developed by the author for dealing with such scenarios at the time of the above workshops, more research work was required by the author in this area, it was concluded following the third workshop that more comprehensive and detailed guidance was required for dealing with disagreements of opinion in a systematic and scientific way.

Fault 3 - The items that may trigger the Periodic Review element of the methodology:

The third fault identified with the guidance documentation provided with the methodology related to the Periodic Review activities of Step 10 of the Quality Risk Management process. One GMP Inspector at the PIC/S workshop pointed out that the guidance provided with the methodology for Step 10 did not address in any clear way what events might trigger a review of a Quality Risk Management exercise that had been carried out on a particular manufacturing process or related item.

The Inspector stated, for example, that a reported Quality Defect or other problem experienced with a medicinal product (or with its manufacturing process) should normally trigger a review of the exercise, but this type of issue had not been addressed

in the guidance documentation for Step 10. The author agreed with this observation, and indicated that this would be addressed in the guidance documentation for the methodology.

Final Remarks:

As a result of the learnings gained when working through the new Case Studies that were developed to test and challenge Version 3 of the methodology, several minor modifications were made to the Worksheet and Laminated Card components of the methodology. (These Case Studies are outlined and discussed above.)

The modifications to the Worksheet involved:

- Inserting explanatory text into Steps 5, 6 & 7 of the worksheet in relation to the need to critically evaluate each GMP control before any Severity, Probability of Occurrence or Detection rating is assigned to a Potential Negative Event associated with that control;

- Inserting additional explanatory text into Step 1 of the worksheet in the section titled Process Map or Schematic in relation to the comprehensive data that is required to be assembled on the Item under Study at the beginning of the exercise

- Inserting a more explicit reference in Step 1 of the worksheet for the need to document all pertinent assumptions that are being made in relation to any part of this Quality Risk Management exercise

- Inserting an explicit reference in Step 4 of the worksheet for the need to consider any available information on near miss incidents in relation to the Item under study

- Inserting an explicit reference in Step 4 of the worksheet for the need to screen all potential negative events in order to identify those potential negative events that should be onward processed through the remaining steps of the Quality Risk Management process. (The modified Quality Risk Management process as outlined

above provides detailed information on how this screening activity should be performed.)

- Providing clarification text into Step 5 of the worksheet to explain that when there is more than one effect identified for a potential negative event, the Severity rating that is assigned to the effects of that potential negative event should reflect the most serious of those effects.

- Changing the text in the header of Step 10 of the Worksheet to read "What communications are required arising out of this QRM exercise, and when will this exercise be reviewed or revisited? This text was considered to more accurately reflect the purpose of this Step than the header for this Step used in Version 3 of the Worksheet.

- In Step 10 of the Worksheet, making reference to the fact that the Periodic Review activities of Step 10 represent a plan for the continuous improvement of the Quality Risk Management exercise.

- Inserting guidance into the section on Periodic Review activities in Step 10 of the Worksheet on what may be recorded in this section.

- Correcting a number of typographical errors that were present in Version 3 of the Worksheet.

The modifications made to the Laminated Card involved the correction of a number of typographical errors that were present in Version 3 of the Laminated Card, as well as clarifying the meaning of the Remote Probability of Occurrence Rating shown on the card. The revised wording read "The Pot. Neg. Event is Very Unlikely to Occur, or is Extremely Unlikely to Occur." (This was the original intent of the Remote Probability of Occurrence rating, but the latter part of this definition had inadvertently been omitted from the first version of the Laminated Card in error.)

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Chapter 5

Subjectivity and Uncertainty during Quality Risk Management activities

Note: Before embarking on developing the final version of the Quality Risk Management methodology, the learnings gained during all of the testing and evaluation work carried out to date in relation to problems of subjectivity & uncertainty were reviewed. This was with a view to incorporating specific and practical strategies into the methodology to counteract such problems. This chapter presents the findings and results in this regard.

5.1 Sources of Subjectivity and Uncertainty in Quality Risk Management

During each of the development and testing stages of this Quality Risk Management methodology, problems relating to subjectivity and uncertainty issues were experienced. Such problems were expected to arise during this research, given the many references in the literature to the subjective and uncertain nature of Risk Management for pharmaceutical applications and in other areas, (9, 26-28, 44, 46, 86-88).

As discussed in Chapter 1, uncertainty is generally unavoidable, given the widely accepted definition of risk[7], which includes a probability factor for the occurrence of a hazard or harm. With respect to problems of subjectivity, this is acknowledged as an issue in many publications (9, 46, 27-28, 87) including ICH Q9, which explains how "each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm" (9).

Kaplan and Garrick (77), in their 1981 paper on risk definitions and related concepts, demonstrate how risk is a concept that is relative to the observer, explaining how risk is thus not absolute, but rather is "a subjective thing – it depends on who is looking."

Another factor that can contribute to subjectivity in risk management activities is the (sometimes) poor use of risk-related terminology. As discussed in Chapter 1 of this thesis, the terms 'risk' and 'hazard' are often (incorrectly) used interchangeably, when

[7] Risk is defined in the ISO/IEC Guide 51:1999 as "the combination of the probability of occurrence of harm and the severity of that harm".

they in fact represent quite different things. Using important terms such as these interchangeably can lead to different people having different understandings about what is being discussed and assessed during risk management activities.

One of the most significant sources of uncertainty and subjectivity in Risk Assessment activities is the ***probability of occurrence*** factor that is often used when estimating risks. Many definitions of risk include a probability or possibility factor for hazards, and as explained in Chapter 1, the probability of occurrence of an event is an item that has attracted much debate in the literature over the years, and its exact meaning has been a significant source of disagreement among mathematicians.

Despite the above inherent problems, formal efforts were made during this research to reduce the level of uncertainty and subjectivity that may be associated with the outcomes of Quality Risk Management activities. With the use of formal, science-based, systematic and vigorous approaches, it was reasonable to believe that uncertainty and subjectivity can be reduced, and that an increased level of confidence in the results and outputs of Quality Risk Management exercises may be achieved.

Within GMP environments, when such Quality Risk Management methodologies are used as an aid to qualification, validation, and change control activities, two important outcomes should occur:

- Increased assurance in the manufacturing processes and controls which have been validated based on the outcomes of Quality Risk Management exercises;

- Increased assurance that potential quality-related risks associated with such manufacturing processes have been addressed.

As documented in earlier chapters of this thesis, during the testing and development of this methodology, a number of practical workshops were run to investigate the application of this methodology as an aid to qualification, validation, and change control activities. In addition, during each phase of development, the methodology was challenged using a number of practical case studies, which represented real-life, GMP-

related problems and issues, spanning a wide range of areas relevant to the GMP environment.

During this work, it was observed that there were several definite areas within formal Quality Risk Management activities that presented opportunities for addressing problems of uncertainty and subjectivity. These areas can be grouped into two broad categories:

- Brainstorming and other team-based activities, especially those relating to the identification and handling of Potential Negative Events (or Failure Modes);

- Activities relating to the consideration of GMP Controls during Quality Risk Management exercises.

Each of these areas is discussed in more detail in the Sections below. With respect to the former, a detailed Case Study is presented below which demonstrates, at a practical level, how poorly defined brainstorming activities can lead to problems of subjectivity and uncertainty during Quality Risk Management exercises, affecting the outcomes of such exercises.

5.1.1 Problems of Subjectivity & Uncertainty during Brainstorming Activities

In relation to brainstorming activities, included in this category were the activities of identifying and documenting potential negative events and their causes during brainstorming sessions, as well as estimating the probability of occurrence of those causes. Also, the activities of assigning severity and detection ratings to the potential negative event, as well as estimating the risks associated with each potential negative event, were included.

From a review of relevant Risk Management standards and methodologies, and their applications in the literature (9, 29, 31, 45-47, 49, 55, 67-68, 108, 115) and in the author's experience from inspecting manufacturers' Quality Risk Management

procedures and activities during GMP inspections, it was observed that the practicalities of using brainstorming activities for the identification and documentation of potential failure modes, faults or hazards were often not adequately proceduralised. ICH Q9 does not provide any detailed guidance in this specific area, and there is often scant instruction provided in other publications and in company Quality Risk Management procedures on how to actually identify and document potential failure modes during brainstorming sessions, beyond mainly conceptual steps (9).

It is considered important that scientific and documented methods be in place for the use of brainstorming techniques, particularly in relation to the identification and documentation of potential failure modes or potential negative events. While this may sound like an obvious thing to ensure, it is surprising how often this is not a clear requirement of many existing Quality Risk Management methodologies. In the author's experience, poorly defined brainstorming techniques, the use of subjective guesswork during brainstorming activities, and an over-reliance on expert opinion during brainstorming sessions without evaluating or documenting the strength of evidence supporting such opinions, often characterise how brainstorming activities occur.

5.1.2 Problems of Subjectivity and Uncertainty in relation to GMP Controls

In relation to GMP controls, the activities in this category included the handling, evaluation and treatment of GMP controls during Quality Risk Management exercises, at both the Risk Assessment and Risk Control stages of the Quality Risk Management process.

The way that GMP controls are identified and handled during Quality Risk Management exercises is important. This is because the qualification and validation outcomes, and the recommendations arising from, Quality Risk Management exercises are directly related to (and usually fully dependent upon) the GMP controls that have been identified and documented during those exercises.

This research found that when there is a lack of procedural rigor in relation to how GMP controls are identified and handled during Quality Risk Management exercises,

this can adversely affect the outcomes and value of such exercises, leading to problems of subjectivity and uncertainty in the results obtained.

For example, during this research it was found that when GMP controls were not assessed or taken into account before probability of occurrence, severity and detection ratings are assigned to potential negative events, there can be a high level of guesswork in the risks that are assessed and determined using such approaches. This can lead to a lack of confidence in the results and outcomes of Quality Risk management exercises. This research also found that when potential failure modes were documented at too high an indenture level in the item under study, (as explained in detail in the Case Study below), there was sometimes confusion between failure modes and their effects. This had a significant and unexpected negative impact upon the GMP controls that were identified during the Quality Risk Management exercises concerned.

To demonstrate the points made above, consider the findings from the following practical Case Study that was developed during the early stages of this research.

5.1.3 Case Study 9 - to demonstrate the implications of the above problems

This Case Study involved the application of Version 1 of the Quality Risk Management methodology to a Change Control proposal raised at an active pharmaceutical ingredient (API) manufacturing plant. This related to the installation of a Filter Dryer in the plant for a particular API process. (Note: the term 'potential failure mode' appears in this case study. This term was used in Version 1 of the methodology; the term 'potential negative event', has since replaced the term 'potential failure mode' in the methodology, from version 3 of the methodology onwards.)

During this Case Study, a workshop was run in which the Quality Risk Management methodology was applied to the above Filter Dryer change control proposal. In the first workshop, 'Low yield' of API material following drying was identified and documented in a brainstorming session as a potential failure mode. A number of potential causes were identified for this potential failure mode, including, breakage of, or damage to, the

stainless steel mesh screen in the filter dryer. It was documented during the workshop that this could result in a physical loss of filtered, solid API material through the screen.

When it came to recording the potential consequences, or effects, of this potential failure mode, the effects were recorded as 'Yield loss, cGMP deviation, economic business effect - unable to meet customer demand". Thus, the potential failure mode and one of the main effects of the potential failure mode were essentially the same - Low yield and Yield Loss'.[8]

As this workshop progressed, it became evident that selecting such a high level potential failure mode significantly limited the extent to which causative factors and their mitigating controls were identified, and documenting the potential failure mode in this manner impacted the outcome of the Quality Risk Management exercise in quite a significant way. For example:

- The potential cause(s) of the actual breakage of, or damage to, the mesh screen were not identified or discussed in any way during the workshop. It is not unreasonable to expect causative factors at this particular indenture level to have been identified, and there was, for example, no discussion during the workshop on whether an incorrectly rated screen (from a pressure perspective) could have been a potential cause for the screen breakage.

- With respect to risk-mitigating controls, the following five risk-mitigating controls were identified during the workshop as being important for addressing the risk associated with this potential failure mode:

    1. Monitor the pressure in the dryer during operation, as a significant pressure drop may indicate a screen failure.
    2. Do a screen integrity check before first batch and after fifth batch.
    3. Do a heavy metals test on the finished API in order to detect screen particles.

[8] The author has also observed this confusion between failure modes and their potential effects during GMP inspections; for example, failure modes such as "out-of-specification batches" may be documented, with their effects listed as "non-compliant product". This problem has also occurred in other workshops using different case studies.

4. Visually inspect the mother liquor for presence of particulates.
5. Ensure the screen is on a regular Preventative Maintenance schedule.

An analysis of the above five controls showed that 80% of the controls were detection-related. The fifth control served as a preventative measure that may have reduced the probability of screen damage or breakage, but to what extent was unknown. Thus, it was clear that the above controls were heavily skewed towards detection as the primary means of addressing the risk posed by the potential failure mode in question. This was likely the result of documenting the potential failure mode at such a high indenture level in the process under consideration, and in a manner that rendered it effectively equivalent to its main end-effects. When this occurred, it meant that the causative factors identified during the workshop were, by definition, quite high level also, and it was noted that preventative controls were not as readily determined than with lower level causative events.

Following this workshop, a repeat exercise was carried out on this same Case Study in which the potential failure mode identification and documentation process provided by the methodology was modified. Here, more care and vigor were applied to this stage of the Quality Risk Management process, and the strategies outlined below were used. As one element of this work, a simple Fault Tree Analysis (45) approach was used during the brainstorming session to help determine causative factors for the selected high-level fault at an appropriate indenture level in the item of interest, that being the filter-drying manufacturing process.

The intent of this repeat exercise was to identify causative events for the high level fault - Low Yield API Batches - via a more vigorous failure mode identification and documentation process, so that these could then be used to identify the potential failure mode and the causes of such at the most appropriate indenture level (from a risk mitigation perspective) in the filter-drying manufacturing process of concern.[9] This

[9] FTA is useful when Failure Modes need to be identified during FMEA and FMECA-based Quality Risk Management exercises. When using FTA methodology, there can be many causative events identified at the same or at different indenture levels in the fault tree and these may contribute to the high level fault. All of these causative events could potentially be considered to be failure modes, and this presents a practical difficulty when FTA approaches are used to identify failure modes, as it can sometimes be difficult to determine where in the fault tree the failure mode(s) should be selected. It was found useful to first select the causes of the failure mode, before identifying the corresponding failure mode from the

approach was designed to ensure that a) any potential failure modes identified and documented during the exercise were adequately differentiated from the high level fault that they related to, and b) that the causative events identified for those potential failure modes were at a sufficiently low indenture level in the item of interest to facilitate meaningful and preventative risk mitigation.

Importantly, as a control between the first workshop and the repeat exercise, the high level fault selected in the repeat exercise during the Fault Tree Analysis activity was the same as the potential failure mode identified in the initial workshop. Note that due to logistical difficulties it was not possible to have the same group of people performing both exercises. This, however, was not seen as an important factor, as these exercises occurred at this early stage of this research, and their intent was to explore how the methodology worked at a basic, operational level, without focusing on the impact of using different teams when performing a Quality Risk Management exercise. (This latter aspect was studied in detail when testing and evaluating Version 3 of this methodology, as discussed in Chapter 4 of this thesis.)

In the repeat exercise, the first causative event identified under the high level fault was "the stainless steel mesh screen in the filter breaks or is damaged". Three causative events were then identified at the indenture level below this one. These three subsequent causative events, each separated by "or" gates in the Fault Tree, were:

- The mesh screen in the dryer is not chemically resistant to the slurry material (including the solvent) being filter-dried.
- The drying process uses an incorrectly rated screen from a pressure perspective, and the screen is unable to withstand the pressure exerted upon it when the filter dryer is at maximum agitation speed and contains a maximum load.
- A wrong screen is installed in the filter dryer during set-up for this API manufacturing campaign.

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fault tree. (The latter will normally be one level above on the fault tree.) The causes of the failure mode can be chosen from the fault tree by examining which causative factors in the tree are most readily suitable for assigning meaningful and practical preventative, detection or other controls to. This is a simple approach, but it has been found by the author to be useable and effective.

The first causative event documented in the Fault Tree under the high level fault was selected as the potential failure mode for the purposes of the exercise, and in the indenture level below this one in the Fault Tree, the three causative factors mentioned above were taken to be the potential causes of that particular potential failure mode. When the above potential failure mode, together with the associated three potential causes, were formally inputted into the Quality Risk Management methodology, substantially different (and more useful) results were obtained compared with those during the initial workshop, even though the issue of concern was essentially the same – low yield API batches.

In the repeat exercise, nine risk mitigating controls were identified for the same low yield problem described in the workshop. These were:

1. Identify the correct pressure rating for the screen by determining (either via developmental batches or engineering calculations) the pressures expected to be exerted upon the screen when the dryer is in operation at maximum agitation speed and at maximum load. Then, ensure that this screen is used in the drying process.
2. Monitor the pressure across the screen in the dryer during operation. A significant pressure drop may indicate a screen failure.
3. Have a second person verify that the correct screen was chosen during set up of the dryer for this campaign.
4. Determine whether the screen material is inert with respect to the material being screened, and ensure that an inert screen material is chosen for this process.
5. Do a screen integrity check before drying the first batch in the campaign and after every fifth batch in the campaign.
6. Do a heavy metals test on the finished API batches.
7. Visually inspect the mother liquor for the presence of gross particulates.
8. Ensure the screen is on a regular Preventative Maintenance schedule.
9. Measure the yield of dried API for each batch. This may detect any gross screen failure, as there will be physical loss of API to the mother liquor.

An analysis of these controls presented a number of important findings. Firstly, an extra four risk mitigating controls were identified for the same low yield problem when

the more vigorous and defined procedures were used for identifying and documenting potential failure modes, in accordance with the strategies listed below. This was an increase of 80% over the controls identified during the initial workshop on the same case study for the same problem.

Secondly, in the repeat exercise, the risk mitigating controls that were identified were much more based on prevention rather than on detection. Four of the nine controls, numbered 1, 3, 4 and 8 above, were preventative in nature, as opposed to only one such control identified during the initial workshop. Similar findings have been observed with other case studies when this same approach was used.

When these preventative controls were considered, the subjectivity and uncertainty associated with assigning probability of occurrence values to the causes of the potential failure mode were clearly reduced, even with this qualitative methodology. This was because we were not now merely guessing probability of occurrence values for the causes of potential failure modes. Rather, there was now a more scientific rationale behind the probability of occurrence values that were assigned.

The above case study demonstrated that, in order to reduce some of the problems of subjectivity and uncertainty discussed above, it was of prime importance that potential failure modes were identified and documented in a scientific manner, using meaningful, consistent and systematic processes. Similar findings were made in another case study run on the methodology, which involved a tablet-film coating process. The research showed also that the improvements made in this part of the methodology significantly improved the way in which GMP controls were identified during the Quality Risk Management exercises, as demonstrated in the above case study. This was important from a qualification and validation perspective.

5.2 Research Methods

5.2.1 The development of specific strategies to address the above sources of uncertainty and subjectivity that were observed during Quality Risk Management activities

As a result of the difficulties experienced during the above and in other Case Studies, and from the experiences gained during the development and testing work performed on this methodology, it became evident that there was a need to develop specific strategies for incorporation into the design of the Quality Risk Management methodology to address the problems of uncertainty and subjectivity that had been observed during Quality Risk Management activities.

Also, there was a need for detailed and clear guidance in the Quality Risk Management methodology in relation to the practicalities of identifying and documenting potential negative events, their probabilities of occurrence, and their associated controls, particularly during brainstorming sessions.

These goals became a major focus of this research as the development and testing of the methodology progressed.

All of the learnings made during the testing activities performed on Versions 1 through 3 of this Quality Risk Management methodology were thus formally reviewed and evaluated. This was with a view to identifying a number of specific design strategies that could be incorporated into the methodology to address the problems of subjectivity & uncertainty described above.

A pre-requisite for this work was that any strategies identified would have to be easy-to-implement and relatively simple in nature, in order to encourage their use by users of this Quality Risk Management methodology.

5.3 Results & Discussion

The result of the above work was a set of documented strategies that were incorporated into this Quality Risk Management methodology. These strategies were specifically designed to help reduce the level of guesswork, subjectivity and uncertainty associated with the Quality Risk Management exercises performed using this methodology.

The strategies related mainly to the identification, documentation and assessment of potential negative events and GMP control activities during the Risk Assessment and Risk Control stages of the methodology. Several of the strategies also related to addressing human behavioural issues which, as the following sections show, have the potential to adversely impact the outcomes of Quality Risk Management exercises.

These strategies, outlined below, were designed to increase confidence in the results of the Quality Risk Management exercises performed with this methodology, whilst at the same time facilitating more meaningful and value-adding Quality Risk Management exercises for qualification, validation and change control activities generally. While the strategies were science-based and qualitative in nature, reflecting the qualitative nature of this methodology, many were actually based on common-sense approaches. (Often, however, such approaches have been overlooked, or have not been developed appropriately, by the current Quality Risk Management methodologies that are available.)

Each of these strategies is presented below, using the following format:

- The number assigned to the strategy & the general area to which the strategy relates are stated;
- The actual strategy is then stated - this is shown in bulleted, italicized and bold font;
- Relevant background information on the strategy is presented;
- Information is given on how the strategy was formally incorporated into the Quality Risk Management methodology.

5.3.1 Strategy No. 1 - General Brainstorming Activities

- ***Prepare for better brainstorming during Quality Risk Management activities, by ensuring that documented and formal guidance is in place for carrying out brainstorming sessions.***

5.3.1.1 Background Information on this Strategy:

Brainstorming is a widely used component of Quality Risk Management processes and methodologies, and it is an effective method to determine not just what might go wrong with the Item under Study, but also the probability of such events occurring. It is often used throughout the Risk Assessment and Risk Control activities, when estimates of risk are being arrived at, and when GMP control issues are being considered as a means of mitigating risk.

It is important, therefore, that any factors which can introduce bias, error or uncertainty into brainstorming activities be counteracted. This research has found that brainstorming is often not formally or adequately proceduralised in current Quality Risk management methodologies, and formal training is often not provided in this area to users of Quality Risk Management methodologies that make use of brainstorming. There is also generally little guidance provided in the current pharmaceutical literature or elsewhere on how to actually perform or to manage brainstorming sessions for GMP environments.[10] As a result, brainstorming sessions can often be poorly structured, not science-based, and inconsistent in approach.

Researchers such as Slovic (94), Kahneman (92) and Tversky (93) have shown that probability judgements made during expert elicitation and brainstorming activities are susceptible to problems of uncertainty, as a result of what are called *heuristic-based behaviors*. (Heuristics are akin to cognitive rules of thumb, which can influence how

[10] During 2005 and 2006, the author asked senior QA personnel within six multinational pharmaceutical manufacturing companies which used formal risk management methodologies as part of internal Quality Assurance activities, whether their procedures allowed for brainstorming as a means of identifying failure modes, faults or hazards, and if so, whether there were documented and detailed instructions in place for how such brainstorming was required to be carried out. In all cases, brainstorming could be used as a means of identifying failure modes, faults or hazards, and in all cases, there were no documented instructions in place for how such brainstorming was to be carried out.

individuals make judgements in the face of uncertainty. They are discussed in detail in Section 5.3.3 below.)

As explained by Morgan, in the widely accepted 'subjectivist' school of probability, the probability of an event is a measure of the person's degree of belief that it will occur (89). Morgan also discusses how experimental psychology research has found that "in most cases, experts and laypersons do not carry fully formed probability values and distributions around in their heads". Rather, "they must synthesise or construct them when an analyst asks for them (89)."

Therefore, brainstorming activities that are well designed and science-based present opportunities for reducing the uncertainty that can arise during this 'synthesis' stage, when experts and other persons are requested to provide an informed opinion on the probability of an uncertain event occurring.

5.3.1.2 How the above Strategy was implemented in this Quality Risk Management methodology:

Detailed and practical guidance for carrying out brainstorming sessions during Quality Risk Management exercises was developed and documented. The starting point for the development of this guidance was to review (and learn from) what was already published in various research fields that were useful and applicable to the area of brainstorming activities. The areas of research reviewed in this regard generally related to group and individual behavioural psychology, such as human psychology (126, 130, 131), cognitive psychology (92-93), experimental psychology (94, 122), as well as risk and policy analysis (89, 100), human reliability analysis (98, 104, 106), weather and other types of forecasting (101), and group behaviour & meeting management (132). Useful learnings and information were also derived from practical training the author and his managerial colleagues at the Irish Medicines Board had received during 2005, on understanding group dynamics, group behavioural psychology and people management issues (133).

The brainstorming guidance that was developed was directed at both the team leaders of Quality Risk Management exercises and at the participants of such exercises, because it was important that everyone involved in the exercise knows how the brainstorming sessions are to be executed, managed and run.

The above guidance is contained within a *Training & User's Manual* that has been developed for users of this methodology. The structure and contents of this Training & User's Manual are described in detail in Chapter 6 of this thesis.

The guidance discusses how, during brainstorming sessions, the person assigned as *Team Leader* for the Quality Risk Management exercise at hand is expected to facilitate the session, and has authority for managing all aspects of the session. In this regard, the key activities expected of the Team Leader are described, such as stating the ground-rules for the session, and explaining what work activities are expected of the participants during the session. There is also guidance provided on how the Team Leader should ensure that the session is designed so as to allow different team participants to express their views and thoughts in ways that suit them best. There is guidance on how the ideas, comments and suggestions which are put forward during the brainstorming session are to be handled and recorded, and with respect to GMP controls, there is guidance on the need to critically evaluate all of the identified GMP controls for their potential role in either risk control or risk reduction.

At an appropriate stage during the brainstorming session, the guidance explains how the Team Leader should stop the discussion and initiate a decision-making process in relation to the questions of interest. This could be in relation to which of the potential negative events that were suggested or proposed should formally be processed through the remaining steps of the Quality Risk Management methodology, or which GMP controls might usefully be employed to mitigate or to control a certain risk.

In relation to Step 4 of the Quality Risk Management process, when selecting the potential negative events for formal assessment through the remaining steps of the methodology, the guidance discusses how, in an ideal situation, all of the proposed or suggested potential negative events would be selected for formal assessment. However,

given the rigorous and highly formal nature of this Quality Risk Management methodology, and given its design intent, the guidance explains how it is often more appropriate (and indeed practical) to select only the most important potential negative events for formal study. The guidance document addresses how this is to be achieved.

5.3.2 Strategy No. 2: Disagreements and Differences of Opinion during Brainstorming Activities

- ***Prior to commencing brainstorming sessions during any step of the Quality Risk Management process, ensure that there are documented mechanisms in place to deal with any disagreements and differences of opinion which may occur, and ensure that all team participants are made aware of these mechanisms.***

5.3.2.1 Background Information on this Strategy:

When significant disagreements or differences of opinion arise during brainstorming sessions, it is considered important that the methodology provides clear guidelines for dealing with such issues, and that those guidelines are understood and accepted by all team members. For example, there may be significant uncertainty associated with the likelihood of the cause of a potential negative event occurring. Even scientific experts in the area of interest can disagree strongly in this regard (89, 100). This can be an important source of uncertainty during Quality Risk Management exercises, especially when the team performing the exercise comprises of more then one acknowledged expert on the item under study or area of concern.

Obviously, the more people that are on the Quality Risk Management team, the greater the chance that disagreements and differences of opinion will arise. This problem can be compounded by having both expert and non-expert people on the team, as experts might not appreciate the opinions of those who may not be as technically familiar as they themselves are with the item under study, or in the area in question.

One option, of course, is to limit the size of the Quality Risk Management team, and/or to limit the number of so called 'experts' (with respect to the Item under study in the

Quality Risk Management exercise) that are on the team. There is some justification for having just one expert (in relation to the Item under study) in the team. In the EU, for example, only one Qualified Person (QP) is required to certify batches of medicinal products for release – there is no requirement to have more than one QP discuss or debate batch certification issues for each batch before certification and release (6, 20, 24, 25). A QP is a person who may reasonably be regarded as being an expert with respect to the product being certified before release, and its manufacturing process.

The size of the Quality Risk Management team should thus ideally represent a balance between the need to ensure that the team is adequately multi-disciplinary in composition, that it has the necessary expertise in relation to the item under study, and that it is not too large.

Disagreements between experts may occur for many reasons. Not only might experts differ in their technical interpretation of the same scientific data and evidence, disagreements may also arise because they may "view the problem from very different perspectives (89)." Research performed in relation to the health effects of air pollution has demonstrated that when experts from different disciplines and fields were employed (such as inhalation toxicology, clinical practice, lung physiology and epidemiology scientists) to assess the effects of air pollution on health, they all had "very different perspectives on the impact of specific air pollutants on health (100)." In addition, uncertainty was observed in the decision-making processes of those experts, possibly because people frequently hold "direct or indirect stakes in the outcome to the question, and thus, their judgements may be influenced by motivational bias, consciously or unconsciously (89)."

Numerous approaches have been used to overcome the uncertainty which can arise when making decisions relating to probability of occurrence values. For example, as a precautionary measure, some FMEA-based applications of Quality Risk Management (44, 51) require the highest possible probability of occurrence value to be assigned to events when the actual frequency of occurrence is not known. (This also occurs with detection ratings in such methodologies.) This approach, however, is not regarded by this author as scientifically sound, as the magnitude of the resulting risks (or the Risk Priority Numbers) that may be generated using such an approach can be greatly over-

estimated. This can then distort the outcome of the Quality Risk Management exercise, leading towards risk mitigation and validation activities that may have little scientific basis.

Other approaches combine in some way the various opinions put forward during brainstorming sessions, perhaps by averaging those opinions or values, or by assigning different weights to opinions, depending on who (expert or non-expert) gave the opinion (51). A number of methods have been developed to assign such weights, and scoring procedures, for evaluating the credibility of experts involved in providing opinions and judgements on questions such as event probability, have also long been available (89). In some fields, for example, a widely used scoring rule for probability estimates is the *Brier* score, developed in 1950 (101). Other researchers such as Matheson and Winkler have developed their own scoring approaches for evaluating assessors of continuous probability distributions (102).

Morgan has assessed the findings from many of the scoring tools that have been developed and has concluded that "the one consistent finding across all elicitation techniques that have been examined is a strong and consistent tendency to over-confidence" in the results of the scoring (89).

A third approach sometimes adopted is one in which the primary risk analyst (or perhaps the Quality Risk Management team leader) considers each differing opinion on its merits, and then makes a "best judgement" call on the probability of the event (89).

There are merits with each of the above approaches, and at this time, no one approach has been shown to be the most effective.

The learnings gained from the above research were used to develop practical guidance in relation to dealing with disagreements and differences of opinion that may occur during Brainstorming sessions. This is discussed below.

5.3.2.2 How the above Strategy was implemented in this Quality Risk Management methodology:

Detailed and practical guidance was developed for how disagreements and differences of opinion are to be dealt with during brainstorming sessions. This guidance is principally directed at the team leaders of Quality Risk Management exercises, as it is usually their responsibility to ensure that such disagreements and differences of opinion are managed in a scientific and fair manner. It is also useful (but not essential) for all team members to be familiar with this guidance.

The guidance sets out in practical, systematic terms, the actions required of the Team Leader when disagreements or differences of opinion occur. It explains how there can be occasions where the differences of opinion have no substantial effect on the outcome of the exercise, and when this is the case, it states what actions the Team Leader should take.

The guidance also addresses situations in which the differences of opinion or disagreements do have a substantial effect on the outcome of the Quality Risk Management exercise, (e.g. where differing opinions result in a risk being judged to be either Acceptable or Unacceptable). Here, the opinions of the different persons on the team should not be combined to produce some average result, because, as Morgan demonstrated, such differences in opinion provide "important information about the problem that should not be quickly discarded (89)."

Guidance is also provided to assist the Team Leader in resolving the dispute, and a clear strategy in this regard is presented for the Team Leader to follow.

When a decision has been reached during the Brainstorming session on the item of dispute, the guidance addresses how this is to be recorded and what Periodic Review activities, if any, might be required to revisit the issue at a later date. The guidance also discusses whether there may be a need to have scientific studies initiated to better understand the issue of dispute following the Quality Risk Management exercise. (This could, for example, relate to performing scientific studies into the failure rate of an item of equipment for a specified reason or via a specified mechanism.) The guidance also addresses key Risk Communication activities in relation to the item of dispute, where required.

The above guidance is contained within the aforementioned *Training & User's Manual* that has been developed for users of this methodology. The structure and contents of this Training & User's Manual are described in detail in Chapter 6 of this thesis.

5.3.3 Strategy No. 3: Addressing the challenges presented by Human Heuristics during Brainstorming and other team-based activities

- ***Ensure that brainstorming and other team-based activities are designed to counteract the potential adverse influences of human heuristics that may lead to problems of uncertainty and subjectivity in decision-making and judgement.***

5.3.3.1 Background Information on this Strategy:

Heuristics are cognitive behaviors. They come into play when people make judgments in the presence of uncertainty. While the ways in which these behaviors are manifested is still the subject of much research, there is much evidence in the literature that heuristics are a source of significant bias and errors in judgment (92-94, 98, 100).

During Quality Risk Management activities, when identifying potential negative events and their probabilities of occurrence during brainstorming sessions, it is important to design controls and features into brainstorming activities that serve to reduce the potential adverse effects that human heuristics may have when judgements are being made or when opinions are being offered. This is because there is usually some level of uncertainty associated with judgments and opinions related to probability and risk.

Kahneman, Slovic and other researchers have shown that heuristics can sometimes lead to biased outcomes and errors when judgements are being made or when opinions are being offered (92-94). Three of the main heuristics described below:

- **The Heuristic of Availability:**

This heuristic affects how people estimate the probability of an event occurring. As Morgan explains, a person's probability judgement is often determined by "the ease with which [people] can think of previous occurrences of the event", or the ease with which they can imagine the event occurring (89).

Research has shown that people find it easier to recall or imagine dramatic, uncommon events (such as deaths from botulism) over more mundane, common events (such as deaths from stroke) (89). This can cause people to sometimes over-estimate the frequency of an event where recall or imagination are enhanced, and to under-estimate the frequency of an event where recall or imagination are reduced. In contrast, people tend to make reasonable estimates of event frequencies when their "experience and memory" of observed events corresponds fairly well with their actual frequencies (89).

- **The Heuristic of Representativeness:**

This heuristic also affects how people estimate the probability of an event occurring. Here, a person's judgement about probability is often influenced by one "expecting in the small behaviour that which one knows exists in the large" (89).

Thus, when tossing a coin six times, where H stands for *Heads* and T for *Tails*, people tend to rate as more likely the sequence *HTHTTH* than either of the sequences *HTHTHT* or *HHHTTT*, even though all three sequences are equally likely. This is because, from one's larger experience, people know that the process of coin tossing is random, and the sequence *HTHTTH* looks more random than the other two. This phenomenon is sometimes referred to by what Kahneman and Tversky call "the belief in the law of small numbers" (92).

The heuristic of representativeness is known to affect how people estimate the probability of an event occurring in another way also. When this heuristic is in operation, people can pay too much attention to the specific details, ignoring or paying insufficient attention to important other information which may be known to them. Research has shown that people tend to ignore or forget important

probability-related information, when they have been given other specific information which is worthless to the question at hand (89).

This heuristic may manifest itself in other ways too, not just in relation to probability decisions. Consider, for example, a failure in a packaging process which results in some packs of an SSRI[11]-based medicinal product being released without a Patient Information Leaflet. When a Quality Risk Management team is assessing the risk presented by such a failure, it can be dangerous to expect in the small behaviour that which one knows exists in the large. In this regard, the fact that many medicinal products may be dispensed in Ireland without a Patient Information Leaflet being provided to the patient by the pharmacist or physician should not be taken as justification for assessing the risk as being low or insignificant during the Quality Risk Management exercise at hand. This is because with products such as the SSRIs, which are indicated to treat moderate to severe depression, it is absolutely imperative that each patient taking the product (or their parent/guardian), has up-to-date information on the potential side effects of their medicine, (such as suicidal thoughts in the case of SSRIs), and on the risks associated with the product. A practical Case Study in this regard is discussed further below.

- **The Heuristic of Anchoring and Adjustment:**

Another heuristic that affects how people make decisions, such as when estimating the probability of an event occurring, is the heuristic of anchoring and adjustment.

When this heuristic is in operation, people's judgement can be heavily influenced by the first approximation of the value or quantity that they think of or hear. Experimental psychology research has shown that the first approximation of the value or quantity that a person may think of or hears can become a natural starting point for that person's thought process (92-93).

This first approximation of the value or quantity is termed an 'anchor' in the person's thought process, and the magnitude of this value or quantity is known to

[11] SSRI stands for a class of drugs called Selective Serotonin Re-uptake Inhibitors

influence any subsequent adjusted values or quantities for the item that is being estimated.

Research by Kahneman and Tversky has demonstrated that the magnitude of this anchor is critical (92-93). When adjustments of the initial value or quantity are made in an effort to arrive at a more accurate answer, for example with the availability of new or more information on the item under study, these adjusted values or quantities are usually biased towards the magnitude of the anchor value or quantity.

5.3.3.2 How the above Strategy was implemented in this Quality Risk Management methodology:

Detailed guidance was developed for how the adverse effects of the above heuristics may be counteracted during brainstorming and other team-based activities, and in decision-making in general.

This guidance is principally directed at the team leaders of Quality Risk Management exercises, as it is usually their responsibility to ensure that these considerations are taken into account during Quality Risk Management exercises. It is also useful (but not essential) for all team members to be familiar with this guidance.

This guidance is summarised as follows:

At the beginning of the first brainstorming (or other team-based) session during the Quality Risk Management exercise, the Team Leader should briefly explain to the team the ways in which cognitive heuristics are thought to affect human judgement and decision-making. Research has shown this approach to be useful, as explaining "what is known about the psychology of judgements made in the face of uncertainty" has proven beneficial (100). In this regard, the Team Leader may base his or her comments and statements on the information provided above in relation to the heuristics of availability, representativeness and anchoring & adjustment.

Then, as the Quality Risk Management exercise progresses, the Team Leader should consider carrying out the following actions at the appropriate time-points during brainstorming and other team-based sessions:

- When a potential negative event (or of its causative factors) are under discussion, taking into account the *heuristic of availability*, and in order to reduce the uncertainty associated with probability-related decisions or estimates made during brainstorming and other team-based sessions, the Team Leader should ask the team if there is anyone on the team who has had direct experience of the potential negative event or of its causative factors.

- If the team has such a person, and if he or she is likely to have learned of the event whenever that event occurred in the past, and if he or she is also able to recall actual real examples of such events, then that person's opinion on the probability of occurrence of the cause of the potential negative event should be considered to be more reliable than that of others on the team. Thus, the Team Leader should indicate to the team that that person's opinion will be used when assigning a rating to the probability of that causative event, unless there is a substantial reason not to do so.

    - An example of such a person would be a long-standing supervisor on a carton packaging line who would have had direct experience of dealing with packaging component handling problems on the line. If this person is likely to be able to recall the events when packs were inadvertently packaged without Patient Information Leaflets (PILs) on the packaging line, then this person is likely to be a suitable person to estimate the probability of such packaging problems for that line or for similar equipment.

    If there is no one on the team who fits the above description, it may be possible to seek out a person within the company who is likely to fit this description, so that that person's opinion of the probability can be sought. The Team Leader should coordinate the required actions in this regard.

If no person can be identified who fits this description, the Team Leader should document in a note that the probability which was assigned to the cause of the potential negative event was an estimate without reliable direct experience. Such notes should be attached to the Worksheet associated with the Quality Risk Management exercise, so that they can be reviewed during the Periodic Review activities on the exercise.

- With respect to the *heuristic of representativeness*, in order to reduce the uncertainty associated with probability decisions which are made during brainstorming or other team-based sessions, the Team Leader should ensure that the team focuses its attention on the item under study, and is not too heavily influenced by the expected behaviour of the larger class of objects that may contain the item under study, unless there is good reason to do so.

  To demonstrate this by way of an example, the Team Leader may discuss with the team the known problem of particulates in injectable medicinal products. One source of particulates in such products is the coring of the rubber stopper closures on vials, when a lyophilised injectable powder product is reconstituted with a diluent which is added to the vial via a transfer needle. One's wider experience may suggest that coring problems of this nature are prevalent with all such products, and that particulates are to be expected following reconstitution. However, if a Quality Risk Management exercise was being performed on such a product, it would be important for the team to focus on the exact product of concern, not just on the broad category of product. This is because the actual stopper and needle components used in the product of concern, the reconstitution instructions stated in the product literature, and the presence of a filtered needle in the pack, may all be important factors to consider before estimating and evaluating the risk posed by stopper coring problems with such a product.

- Again with respect to the *heuristic of Representativeness*, the Team Leader should ensure that the team focuses its attention on the relevant information at hand when assigning a probability value or probability rating to an event. Other information which is at hand but which is irrelevant to the question of interest should be ignored.

This gets over the potential problem of team members paying too much attention to specific pieces of information that may be interesting but not relevant to the specific issue being discussed at that time, while ignoring or paying insufficient attention to certain background information which may be more important, such as component failure rates, etc. As discussed above, research has shown that people tend to ignore or forget important probability-related information, when they have been given other specific information that is worthless to the question at hand (89).

- With respect to the *heuristic of anchoring and adjustment*, before any ratings or values for the probability, severity or detectability of a potential negative event, its causes or its effects, are discussed during the brainstorming or other team-based session, the Team Leader should do the following:

    - He should instruct the team that no initial probability, severity or detectability opinions are to be verbalised by anyone on the team until each member of the team has a) had an opportunity to consider the issue and the facts for him or herself, b) formed their own initial opinion or judgement on the issue at hand, and c) privately written their opinion or judgement down.

    - A round table discussion of the opinions or judgements should then occur, and every team member should be encouraged to disclose what they had recorded.

    - While this strategy will not likely overcome anchoring effects as a result of the initial value or opinion thought of or formulated by the individual in his/her own mind, it may help to reduce some of the potential adverse effects caused by the heuristic of anchoring and adjustment. This is because each team member will have had space and time to form their own opinion or judgement before hearing that of other team participants.

It should be noted, however, that in the author's experience, and from a detailed review of the literature, it is difficult to counteract the potential adverse impact of the heuristic of anchoring and adjustment when such judgements and decisions are

being made. This is because one's own thought processes, which are the principle means by which the effects of this heuristic are realised, cannot easily be controlled, and simply thinking of an answer to the problem at hand, may play an important part in the operation of this heuristic. However, it is possible that some of the uncertainty which may be associated with probability and other decisions during brainstorming sessions as a result of this heuristic may be overcome.

The above guidance is contained within the aforementioned *Training & User's Manual* that has been developed for users of this methodology. The structure and contents of this Training & User's Manual are described in detail in Chapter 6 of this thesis.

5.3.4 Strategy No. 4: Ensuring Pertinent Assumptions are taken into account during Quality Risk management exercises

- ***During brainstorming and other team-based activities which may occur during Steps 1 through 8 of the Quality Risk Management process, the Team Leader should ensure that any pertinent assumptions that are made relating to qualification and validation issues, and which may be significant for specific potential negative events, are discussed and clearly documented during such sessions.***

5.3.4.1 Background Information on this Strategy:

Problems of uncertainty and subjectivity in the outcomes of Quality Risk Management activities may be exacerbated when assumptions relating to the item under study are not properly documented or openly recognised. For example, assumptions relating to the qualification status of items of equipment, or of maintenance activities for items of equipment that serve to maintain qualification or calibration status, may be important when equipment-related potential negative events are being identified during Step 4 of the Quality Risk Management process. These assumptions should be stated up-front and clearly documented during the Quality Risk Management exercise.

This not only facilitates the exercise at hand, it also ensures that the team performing a review of the Quality Risk Management exercise at some later date as part of Periodic Review activities can consider those assumptions in light of the information at hand at that future time-point.

5.3.4.2 How the above Strategy was implemented in this Quality Risk Management methodology:

A formal requirement to document any pertinent assumptions which may be relevant to the exercise at hand was incorporated into Step 1 of the Quality Risk Management worksheet.

In addition, this issue was addressed in a general Guidance presentation which has been prepared on the methodology, and which forms part of the aforementioned Training & User's Manual on the methodology.

5.3.5 Strategy No. 5: Ensuring that Potential Negative Events are correctly identified & documented during Quality Risk Management exercises

- ***During brainstorming at Step 4 of the Quality Risk Management process, the team should formally review each proposed potential negative event at the time it is proposed, to ensure that a) it and its effects are not essentially the same, and b) that each proposed potential negative event is documented at an indenture level in the item or system under study that can provide meaningful, causative events that lead to appropriate risk mitigation and control.***

5.3.5.1 Background Information on this Strategy:

A common problem observed during this research (and also in GMP inspections performed by the author) when Quality Risk Management exercises were performed was that, during brainstorming sessions, if there was a lack of clear procedure and rigor applied to the process of identifying and documenting potential negative events, in some cases, potential negative events had been documented that were essentially the same as

their effects, or, they were identified at too high an indenture level in the item or system under study to be of value in risk mitigation and control.

The above Case Study in Section 5.1.3 of this Chapter provides a detailed, practical example of the above. This is also discussed in the paper from this research published in the Journal of Validation Technology in February 2007 (125).

The above lack of procedural rigor was found to have a significant and unexpected negative impact on the outcomes of the Quality Risk Management exercises in question.

For example, this sometimes resulted in confusion between Potential Negative Events (or failure modes) and their effects. Also, some Potential Negative Events were documented at an indenture level in the item or system under study that made it difficult to identify meaningful, risk mitigating GMP controls.

In this regard as well, it was observed that some proposed Potential Negative Events had so many potential causes, that the Quality Risk Management exercise became practically unmanageable when it came to working through the Qualification & Validation stage of the Quality Risk Management process. For example, proposed Potential Negative Events such as 'Out-of-Specification Batches' or Loss of Sterility Assurance' can have so many causes in a manufacturing environment that the Quality Risk Management exercise becomes very large and difficult to work through in practice.

Potential Negative Events should thus be specific and narrow enough in scope so as to facilitate a workable Quality Risk Assessment exercise. As a guide, this research found that if more than five potential causes are identified for any proposed Potential Negative Event, then the Potential Negative Event is probably at too high an indenture level in the system or item under study, and, if possible, should probably be broken down into more specific Potential Negative Events.

With regard to the confusion that was experienced in some workshops run with this methodology between potential negative events (or failure modes), their causes and effects, it was not entirely unexpected that this might occur during Quality Risk Management exercises. This was because the potential effect of a potential negative

event identified at one level in the system under study may be considered to be a potential negative event itself at a higher indenture level in the system under study.

Also, potential negative events identified at one indenture level may become potential negative events causes at a higher indenture level (44, 52). This highlights the important of training for users of a formal methodology such as this one.

5.3.5.2 How the above Strategy was implemented in this Quality Risk Management methodology:

Guidance in relation to the identification and documentation of potential negative events at Step 4 of the Quality Risk Management process was documented, and this was included in the aforementioned general guidance presentation that has been prepared on the methodology, and which forms part of the aforementioned Training & User's Manual on the methodology.

This guidance addresses how to differentiate between potential negative events and their effects, and how to identity the appropriate indenture level in the item or system under study for identifying meaningful, risk mitigating GMP controls. (Stamatis, 2003, also provides a useful discussion in this regard (44)).

This Guidance also discusses the usefulness of posing the following key questions to the team performing the Quality Risk Management exercise at Step 4 of the Quality Risk Management process.

- What can go wrong?
- What are the potential effects or consequences of this going wrong?
- Is the potential negative event, as proposed, the same as its potential effects? If the latter is the case, what is the true failure mode relating to those effects?
- Approximately how many causes might this potential negative event have?

These simple questions are intended to force the Quality Risk Management team to differentiate between proposed potential negative events and the effects of such. (This approach was found to be useful during this research, when performing actual Quality Risk Management exercises.) They also help the team to determine whether the potential negative event may be documented at too high an indenture level in the system or item under study.

In addition to the aforementioned general guidance presentation, the practical Case Study mentioned above was incorporated as an Appendix to that presentation. This was in order to provide users of this methodology with a detailed example of the importance of executing Step 4 of the Quality Risk Management process correctly. Thus, this above Case Study demonstrates the importance of ensuring that each proposed potential negative event represents a true potential negative event in relation to the effects envisaged, that it is not merely the equivalent of those effects written another way, and that it was documented at an indenture level in the system or item under study that permits the identification of meaningful, risk mitigating GMP controls.

5.3.6 Strategy No. 6: Near Miss Incidents

- ***During brainstorming activities at Step 4 of the Quality Risk Management process, the Team Leader should encourage the team to think about Near Miss Incidents when identifying potential negative events***

5.3.6.1 Background Information on this Strategy:

It is well established that, when identifying potential failure modes or negative events in pharmaceutical manufacturing, it is useful to review obvious sources of information, such as data on process deviations, batch rejects, product complaints and quality defects, production problems, qualification and validation incidents, reasons for change controls, etc. However, an area that was found during this research to be one that is often overlooked in formal Quality Risk Management methodologies is the evaluation of near miss events, or potential problem incidents that almost occurred.

This research has found that near miss incidents, when documented correctly, can provide valuable and reliable information on what potential negative events may occur with the item under study, as well as information on their frequencies and causes. This in turn helps to reduce the level of subjectivity and uncertainty that may be associated with the selection of potential negative events during Quality Risk Management exercises, because those potential negative events that were selected on the basis of near miss information will, by definition, be supported by verifiable data.

To make use of near miss information during Quality Risk Management exercises, however, there first has to be in place a culture of reporting near misses within the organisation. In addition, formal reporting mechanisms would have to be in place for such incidents, and these should be integrated as a formal element of the company's Quality Management System, similar perhaps to how deviations are presently reported.

At the present time, in pharmaceutical manufacturing environments near miss incidents are not always documented within a company's Quality Management System. Admittedly, there are no clear EU GMP requirements governing this area at the time of writing (December 2007), and there is currently no clear obligation on manufacturers to formally capture information on near miss incidents within their Quality Management Systems. It is not unreasonable, however, to encourage manufacturers to capture and formally document near miss incidents so that data on these incidents may be usefully used during Quality Risk Management exercises.

5.3.6.2 How the above Strategy is implemented in this Quality Risk Management methodology:

In this methodology, Steps 4 and 5 of the Quality Risk Management process have been designed to require near miss incident information, where available, to be formally considered by the Team performing the Quality Risk Management exercise. The intent here is that the team would review the near miss incident information for potential negative event signals, as well as for data on the likely causes and probabilities of occurrence of such potential negative events.

Guidance in this regard was documented and included in the general guidance presentation which forms part of the Training & User's Manual on the methodology.

5.3.7 Strategy No. 7: Compiling comprehensive data on the Item under Study

- ***During Step 1 of the Quality Risk Management process, as an aid to subsequent steps of the Quality Risk Management process, the Team Leader should ensure that comprehensive data have been assembled on the Item Under Study.***

5.3.7.1 Background Information on this Strategy:

Some Quality Risk Management methodologies recommend that a map of the process or item under study be generated for participants of the Quality Risk Management exercise. The intention is that such a map would be used to determine where potential failures modes or negative events might occur in the process or item under study (52).

This is regarded as a useful approach, but in the author's experience, and as evidenced from the workshops that were carried out during the development and testing of this Quality Risk Management methodology, process maps sometimes provide only very limited information, and can be of little practical value during Quality Risk Management exercises.

In order to improve confidence in the outputs of Quality Risk Management exercises, this research found that it was useful when comprehensive information was compiled on the Item under Study, so that the Quality Risk Management team performing the exercise could draw upon that information when making decisions on issues such as potential negative events.

This research also found it useful to have defined requirements in place for the type of information and documentation that should be assembled at the beginning of the Quality Risk Management exercise on the Item under Study. If a process map or flowchart of the Item under Study was to be used, it was thus required to be sufficiently detailed and descriptive to ensure that it was of value.

Following the testing performed on the early versions of this methodology, the scope of what was initially considered to be a 'Process Map' was extended so that more comprehensive information was required to be assembled on the Item under Study. It was found that, where possible, the following information and documentation should be assembled on the Item under Study at the beginning of the Quality Risk Management exercise:

- A brief overview of the technology or science underpinning the Item under Study, where applicable.

  During this research, a workshop was carried out in which this methodology was applied to a fermentation-based manufacturing process. A presentation given to the team by the facilitators of the Quality Risk Management exercise on the general principles of fermentation processes was found to be highly beneficial to the other workshop participants. This was important given the fact that the workshop team was multi-disciplinary in nature, and that some members were not technically familiar with the principles of fermentation or with the general technology behind the manufacturing of biotechnology-derived medicinal products. (Similar observations were made during other workshops run on this methodology.)

- The actual (detailed) Master Batch Manufacturing Record or SOP(s) relating to the Item under Study, if applicable.

  For example, if the Item under Study is a supplier approval programme, the SOP in place for this activity should formally be part of the process map for the Quality Risk Management exercise. Note that with highly complex and multi-step processes, it was found that it was more useful to use a schematic or documented overview of the process or Item under Study, rather than the actual detailed Master Batch Manufacturing Record or detailed SOP(s). However, the latter documents were still readily available for consultation, if needed, and these were considered an important resource for the exercise.

- For Change Control proposals, the current process or procedure as well as the proposed process or procedure in outline or flow chart format.

- A list of the equipment as well as the identities of all ancillary equipment relating to the Item under Study. (For example, if the Item under Study is a manufacturing process, and if sampling occurs on that process, sampling equipment and sampling booth facilities should normally be included in the equipment list for the Item under study.)

- Copies of any ancillary SOPs or other documents which are required for the Item under Study, such as SOPs for controlling room environments, etc.

- The known Critical Process Controls for the Item under Study, as well as the in-process tests, the finished product tests, and their specifications or limits.

- A copy of the developmental report(s) on the manufacturing process, where applicable and available, which may show proven acceptable ranges for a manufacturing process, or equipment settings and other parameters (e.g. mixing speeds, temperature ranges, etc.) that were found to be acceptable.

- A listing of the steps in the manufacturing process or in the Item under Study in which human intervention occurs, or is at its highest.

- A listing of deviations, change controls, complaints, reported problems, rejected batches, out-of-specification batches, non-conformance issues, near-miss incidents, etc., relating to the Item under Study and which may be relevant to the exercise at hand.

5.3.7.2 How the above Strategy is implemented in this Quality Risk Management methodology:

Step 1 of the Quality Risk Management process was designed to formally require the above comprehensive information and documentation, where available and relevant, to be assembled on the Item under Study, as an aid to the Team performing the Quality Risk Management exercise. The Team Leader has responsibility for ensuring that this occurs.

In addition, guidance on what information might be included when assembling such comprehensive information and documentation on the Item under Study was documented, and this was included in the general guidance presentation which forms part of the aforementioned Training & User's Manual on the methodology.

5.3.8 Strategy 8: Taking Strength of Evidence into account during Quality Risk Management exercises

- ***During the decision-making activities associated with Steps 4 through 7 of the Quality Risk Management process, the Team Leader should ensure that strength of evidence is considered when expert judgements and informed opinions are offered.***

5.3.8.1 Background Information on this Strategy:

It is of course good practice to make use of informed opinion and expert judgement during Quality Risk Management activities, especially when potential negative events and their probabilities of occurrence are being identified and assessed, and this is a feature of many existing Quality Risk Management methodologies. However, to date, there has been little, if any, guidance developed for users of Quality Risk Management methodologies on how best to elicit informed and expert opinions/judgements, or on the factors which may negatively impact upon the process of eliciting expert judgement and informed opinion.

At a practical level, it is important to seek and assess the strength of evidence for each opinion or suggestion proposed during brainstorming and one-to-one meetings as part of Quality Risk Management exercises. This not only adds rigor to the exercise, it also helps to reduce the level of subjectivity and guesswork that can arise when potential negative events and their probabilities of occurrence are being identified.

During this research, when the various case studies discussed earlier were being developed, the following activities were found to be useful in relation to identifying and assessing the risk associated with potential negative events.

- Seeking the opinions of actual users and operators of the Item under Study;
- Seeking the opinions of those employees or others who were knowledgeable in the item under study;
- Taking into account the concerns of stakeholder groups when considering "what might go wrong" with the Item under study.

The opinions of users and operators of the Item under Study, as well as those of other personnel who were knowledgeable in the item under study were found to be valuable during the Case Study work. In many cases, these people knew very well what could go wrong with the process or activity under consideration, and how this might occur. They were also sometimes in a position to advise on the probability of occurrence of the causes of a potential negative event. In Case Study No. 5, for example, which involved the application of this methodology to a product distribution and recall system at a finished product manufacturer, users of the SAP-based stock control system were in a position to reliably advise on important potential negative events with that SAP system. In Case Study No. 6, in which the methodology was applied to the proposed introduction of ICP-MS equipment into an API laboratory, information from the equipment vendor on the likely mechanisms and rates of vacuum pump failure in the instrument proved valuable for the Risk Assessment-related steps of the exercise.

In relation to importance of taking into account the concerns of stakeholder groups when performing Quality Risk Management exercises, during a Case Study relating to missing patient information leaflets in packs of an SSRI medicinal product, the specific

concerns of regulators were an important source of information when working through that Case Study. Here, before a Severity rating was assigned to the effects of a potential negative event that related to a failure of the packaging line to insert a Patient Information Leaflet into every pack of an SSRI-based medicinal product, regulators at the Irish Medicines Board were consulted for their opinion on the consequences of such a potential negative event for a product of this nature. (The product in question was authorised to treat moderate to severe depression.). This proved valuable, as those same regulators had direct experience of dealing with the outcomes of such products not having the correct and up-to-date Patient Information Leaflet in packs of the product.

Stakeholder consultations can be beneficial in many other ways also during Quality Risk Management activities. For example, if a change has been proposed to roll out a new labelling and livery design for a company's range of medicinal products, practicing pharmacists may usefully advise about the risks of dispensing or usage errors that may be introduced by the change, even when the new labelling is fully compliant with regulatory labelling requirements.

Also important to consider were the findings from research in the field of experimental psychology. Research in this field provides a wealth of information in relation to how people make judgements in relation to uncertain and subjective issues or quantities, and the learnings gained from this research can be useful when performing Quality Risk Management activities. Research by Lichtenstein et al., for example, demonstrated that the more information subjects have about an unknown quantity, the less likely they are to exhibit what is called "over-confidence" in their judgements (126). However, the value of using subject matter experts for obtaining reliable judgements is far from clear at the present time.

Research by Mullen at Carnegie Mellon University in the US, as part of her doctoral thesis on the process of probabilistic estimation, demonstrated that acknowledged experts in an area of study were susceptible to the same influences of cognitive heuristics, such as anchoring and adjustment, as non-experts, though the extent to which they were affected was found to be not as high (130). Other researchers, such as Goldberg, have shown that experts sometimes perform no better than lay people in making judgements relating to their area of expertise (131)!

Three important factors were identified by Faust (134) in 1985 which appeared to influence the ability of experts to make reliable judgements on uncertain quantities in an area of study. These were:

- The availability of a well developed science that provides established scientific theory for the area under study;
- The availability of precise measuring techniques in that area of study;
- The availability of pre-specified procedures and judgement guidelines for decision-making.

Morgan, in his extensive review of the findings of the above and several other researchers in this area found that problems relating to human heuristics "appear more likely to arise in fields involving complex tasks", with limited empirically validated theory (89)."

The above findings are important for the pharmaceutical manufacturing industry. This is because, while this industry is involved in complex manufacturing processes and high technology activities, it is also an industry that is clearly Quality System-based and procedure-driven. It places a high emphasis on the need to use validated measuring and control methods, and over the last decade, there has been an increasing focus on the use of science and science-based control technologies in pharmaceutical manufacturing. The ICH Guideline titled 'Pharmaceutical Development', (ICH Q8), is testament to that (135). As a result, the pharmaceutical manufacturing industry and the GMP environment generally are areas that should be less affected by the above factors when its subject matter experts are asked to make judgements on uncertain quantities in their areas of expertise.

Other research has been performed into how best to elicit opinions and judgements from experts and non-experts, and the findings in this area are also relevant to brainstorming activities during Quality Risk Management exercises. For example, research by Hoch et al, (136) has indicated that asking experts for carefully articulated justifications and reasons for and against their judgements may improve the quality of those judgements.

Again, however, the situation is still far from clear. The Hoch research also demonstrated that subjects' probability judgements were "greatly affected by being asked for reasons" for and against their judgements, and that their judgements were influenced by the type of reason asked for first (89)."

Hoch also found that peoples' judgements were less affected by the type of justification questions asked of them when they were more experienced in the item under study than when than when less experienced. This suggests that, during brainstorming sessions, one should exercise caution particularly when challenging non-expert subjects on their opinions by asking for reasons and justifications for their opinions.

Morgan summarised the situation by stating that "there is some evidence that asking for carefully articulated justification and reasons for and against judgments may improve the quality of judgements", but that more research was clearly needed in this area (89).

5.3.8.2 How the above Strategy was implemented in this Quality Risk Management methodology:

The Quality Risk Management process has been designed to formally require the Team Leader to seek and discuss the strength of evidence pertaining to opinions and judgements given during Quality Risk Management exercises, taking into account the learnings discussed above.

Detailed guidance in this regard was compiled and was included as an Appendix to the general guidance presentation which forms part of the Training & User's Manual on the methodology. This Guidance was designed mainly for leaders and facilitators of Quality Risk Management exercises.

5.3.9 Strategy No. 9: Focussing on GMP Controls during Quality Risk Management exercises

- ***Before any risks are evaluated, assessed or re-assessed using this methodology, and before any Qualification, Validation and Change Control requirements are finalised for the Item under Study, a careful and critical evaluation of the GMP controls pertinent to each risk must be carried out.***

5.3.9.1 Background Information on this Strategy:

This Quality Risk Management methodology is concerned with facilitating risk-based Qualification, Validation and Change Control activities in GMP environments. It was considered important therefore during the development of this methodology that, to achieve meaningful risk-based Qualification & Validation, GMP controls had to be identified during Quality Risk Management exercises that were directly or indirectly linked to the risk under assessment.

This was so that risk-based critical process parameters, critical features or other required outcomes could be determined for each control prior to the design of any Qualification or Validation protocol for the item under study. An ISPE White Paper of March 2005 provided a useful discussion on the importance of this approach (37).

Likewise, in the area of Change Control, in order to meaningfully evaluate, assess and manage the risks which may be presented by a proposed change, it was considered important that GMP controls be identified during Quality Risk Management exercises that may help to reduce or control those risks to an acceptable level. This would have a synergistic effect, in that when a Change Control required some degree of Qualification & Validation work to be performed, the GMP controls identified during the Quality Risk Management exercise would be helpful when designing the necessary Qualification & Validation protocol for the changed process or other activity.

It was also considered important that any risks estimated using this methodology would be free from as much subjective guesswork and uncertainty as possible. In addition to the other strategies mentioned in this Chapter, one way that this could be achieved was

to disallow any estimation or assessment of risk by the methodology before the GMP controls which might influence the magnitude or acceptability of those risks were taken into account.

A major shortcoming of some Quality Risk Management methodologies, in particular those based on FMEA and FMECA, is that there is often much subjectivity and guesswork involved in the process of assigning probability of occurrence, severity and detection ratings to failure modes or hazards when risks are being estimated, and when Risk Priority Numbers (RPNs) are being determined. This point was made repeatedly by industry groups and GMP Inspectors to the author during this research work. (For example, it was made during the Quality Risk Management workshop run with an industry validation group at Cork, Ireland, in November 2005, and during the workshop run with GMP Inspectors at the PIC/S Workshop at Düsseldorf, Germany, in June 2006. (Both of these workshops are discussed in detail in Chapter 4 of this thesis.)

One reason for the above shortcoming is that, often, the current controls that are in place at the time of the Quality Risk Management exercise are not adequately evaluated or taken into account before probability, severity and detection ratings are assigned to failure modes or hazards. This is not only the case during the initial risk assessment activity, but also the case during risk control activities, when revised probability, severity and detection ratings are being assigned to a failure mode or hazard. This can lead to the determination of risks and Risk Priority Numbers which have little scientific basis and which do not reflect the current state of control. The resulting risks that are estimated using those assigned ratings, or the resulting RPNs that are calculated, are prone to a level of uncertainty and subjectivity that generally cannot easily be dismissed or dealt with.

In addition, the next time that a similar Quality Risk Management exercise is performed on the same process or Item under Study, there may be little assurance that a consistent approach will be taken when estimating risks or when calculating RPNs. Thus, during such periodic review activities, one can be unsure how meaningful the results generated from the Quality Risk Management exercise actually are.

5.3.9.2 How the above Strategy was implemented in this Quality Risk Management methodology:

The identification and critical evaluation of GMP controls was made central to the design of the Quality Risk Management process used by this methodology. This was not only in design of the Risk Assessment steps of the process (Steps 4 through 6), but also in the design of the Risk Control stage (Step 7) and the Qualification and Validation stage (Step 8).

This Quality Risk Management process explicitly requires GMP controls to be identified, documented, individually classified (as affecting either probability of occurrence, severity or detection) and critically evaluated before any probability of occurrence, severity or detection ratings are assigned to any potential negative event. For example, in relation to controls that may influence the Severity rating assigned to the effects of a potential negative event, Step 5 of the Quality Risk Management process requires the team to list any *Current Back-up Systems or Redundancy Controls* which may counteract or eliminate those negative consequences should the potential negative event occur.

Then, when a Severity rating is being assigned to those effects, Step 5 requires the team performing the Quality Risk Management exercise to critically evaluate the usefulness of the controls identified in terms of how they may reduce the effects of the potential negative event. Similar requirements are in place in this methodology for the GMP controls that may influence the probability of occurrence and detectability of the potential negative event or its causes.

The worksheet used by this methodology was designed and structured to reflect the above requirements. Thus, Steps 5 through 7 of the worksheet specifically require the team to identify and document GMP controls for all potential negative events processed through the worksheet. Before any risks are estimated and assessed, the worksheet formally leads the team towards carefully considering and critically evaluating any GMP controls that are currently in place for the Item under Study at the time of the exercise. This allows the team to document the influence those controls may have on

the probability, severity and detection parameters for the potential negative event, before any such ratings are assigned to the potential negative event.

Additionally, the Quality Risk Management process developed for this methodology was designed in a way that allows for a wide range of GMP controls to be documented and evaluated for their qualification and validation requirements. This is also reflected in the design of the worksheet that the methodology uses. In this regard, not all controls have to have Critical Process Parameters associated with them in order for their qualification or validation requirements to be identified and documented at Step 8 of the worksheet. Instead, acceptance criteria or other required outcomes associated with a particular control may be documented at Step 8 when there are no obvious Critical Process Parameters associated with the control. This is an important feature of the methodology, as it contributes to its robustness. (See Chapter 8 of this thesis for further discussion in this regard.)

During the workshops and Quality Risk Management exercises performed on this methodology at its various stages of development, this work found that the classification of GMP controls in terms of how those controls related to the Severity (S), Probability of Occurrence (P) & Detection (D) of a potential negative event, and the critical evaluation of those same controls for how they may influence those S, P & D ratings, were extremely useful and important features of the methodology, that set it apart from other methodologies. This applied not only during the initial risk assessment stages at Steps 5 & 6 of the process, but also at the Risk Control stage, at Step 7. This was because, when the above approach was used, there was greater confidence in the S, P & D ratings that were assigned to a potential negative event, and any subjectivity and uncertainty concerns associated with those ratings were reduced.

Conversely, when the above approach was not used, this research found that there tended to be an over-reliance on subjective opinion and guesswork when assigning Severity (S), Probability of Occurrence (P) & Detection (D) to potential negative events, and there was a higher degree of uncertainty over the outcomes of such Quality Risk Management exercises.

In terms of providing documented guidance to users of this methodology on the above features of the methodology, specific and detailed guidance, together with practical exercises, were developed on the classification and evaluation of GMP controls for how they may relate to Severity (S), Probability of Occurrence (P) & Detection (D) considerations. This guidance is included in the general guidance presentation which forms part of the aforementioned Training & User's Manual on the methodology.

Additionally, and recognising the fact that Severity-related controls proved to be a difficult area for users of this Quality Risk Management methodology during a number of the early workshops run on this methodology, extra guidance has been provided in the general guidance presentation on the meaning of Severity-related controls, and practical examples of this are also provided.

The above Guidance was designed not only for leaders and facilitators of Quality Risk Management exercises, but also for all team participants.

5.3.10 Strategy 10: Terminology & Definitions

- ***During Step 3 of the Quality Risk Management process, the Team Leader should ensure that the team agrees on the definitions & meanings of the various terms used in the Quality Risk Management process, and that this terminology is used in a consistent manner thereafter.***

5.3.10.1 Background Information on this Strategy:

During the course of this research, when studying how Quality Risk Management may be applied to qualification, validation and change control activities at a practical level, a number of problems were encountered with some of the terminology used in early versions of this methodology. These problems gave rise to difficulties in completing several of the early Quality Risk Management exercises, and also, there was sometimes uncertainty and confusion observed among team members on what activities were actually occurring at certain points in the Quality Risk Management process, and this was a result of confusing or inappropriate terminology.

For example, the term 'Critical Process Parameter' was found to be easily applied to, or used in, one situation, but often not in another. This term is also used in some FMEA and HACCP-based applications (44, 48-49).

During the workshops and practical case studies performed as part of this research, Critical Process Parameter terminology worked well when applied to process-related controls, such as in-process controls used in batch manufacturing processes. (An in-process control such as the monitoring of solution acidity before a reaction quenching step might have solution pH as a Critical Process Parameter.) However, Critical Process Parameter terminology was found not to work well with other types of controls that are commonly encountered within manufacturing processes and GMP environments. Staff training and supplier qualification, for example, are important types of controls relevant to a variety of situations and activities within GMP environments, but they were not so easily described in terms of Critical Process Parameters when it came to doing so with this methodology. This resulted in problems when applying the Quality Risk Management methodology to help determine qualification and validation requirements for the Item under Study.

Misunderstandings and confusion among the participants of Quality Risk Management exercises on what different terms mean were also observed during the early stages of this work. These issues were seen to impact upon the success of the exercises, and it was observed that this led to problems of subjectivity and uncertainty in the results of such exercises. For example, the inconsistent use of the terms *Risk Analysis & Risk Assessment* lead to misunderstandings among users of early versions of the methodology on what activities were actually being performed under each heading, and what the expected outputs were for the exercises at hand.

In this regard also, it was noted that a number of the terms used in the methodology were not intuitively easy to understand, especially when used in practical situations. The term *Failure Mode*, for example, was one such term, and there was a case for using simpler, more explanatory terminology, even in process-based Quality Risk Management activities which often make use of FMEA-based methodologies.

It was found during this work that it was vital for terminology to be kept as simple and intuitive as possible, and that it is used in a consistent manner throughout the Quality Risk Management process. It was also found that some commonly used terms in Quality Risk Management activities were such that they did not always convey the nature of the activity that they related to. For example, the term "Periodic Review" could more simply be termed "A Plan for Continuous Improvement of the Risk Assessment exercise." While obviously longer, this phrase is probably more explanatory of the activity required.

5.3.10.2 How the above Strategy is implemented in this Quality Risk Management methodology:

The supporting documentation which accompanies this methodology, such as the presentations that describe how the methodology is used and structured in the Training & User's Manual prepared on the methodology, generally explains a lot of the terminology that is used in the methodology. In addition, the terms that relate to the various components of the Quality Risk Management process, such as Risk Analysis, Risk Evaluation, Risk Assessment, are also described and explained in those presentations.

When performing training activities on this Quality Risk Management methodology, there is a requirement for the trainer to review with the trainees the key terminology used in this methodology, and specific training materials have been generated to facilitate this. (Chapter 6 provides detailed information in this regard.)

For example, the term 'Redundancy Control' is used in Steps 5 and 7 of the Quality Risk Management process, and the general guidance presentation in the Training & User's Manual provides detailed guidance on what is meant by a redundancy control, and practical examples are given to demonstrate this. There is also a requirement for trainees to review the guidance and definitions presented in ICH Q9, as much of the terminology used in this methodology was drawn from ICH Q9, where possible.

When this Quality Risk Management methodology was being tested and developed during the various stages of this research, a significant number of changes were made to the terminology that the methodology used. Some of these are described below:

- The term 'Probability Control' was used in early versions of Step 5 of the Quality Risk Management worksheet, but this was replaced with the term 'Preventative Control' in later versions, because the latter was considered intuitively easier to understand.

- The term 'Severity Control', also used in early versions of Step 5 of the Quality Risk Management worksheet, was replaced with the term "Back-up Systems / Redundancy Controls", because the former proved repeatedly problematic for participants during the various workshops that were held on those early versions of the methodology.

- The term 'Failure Mode' was used in the early versions of this methodology, but in several of the workshops run on the methodology, it was found that this term was not intuitively easy for some participants to understand. As a replacement, the term "Potential Negative Event" was adopted to denote "what can go wrong" with, or in, the Item under Study in the Quality Risk Management exercise. This term was immediately preferred among workshop participants, as it was deemed intuitively easier to understand and to comprehend than the term 'Failure Mode'. In addition, the potential negative event terminology was found to be more readily applicable to a wider range of activities and areas.

In this methodology, a Potential Negative Event can be a single event, or a number of individual occurrences leading to a negative outcome. Risks arising from Potential Negative Events are estimated, assessed and controlled via Steps 5-7 of this Quality Risk Management process. Recognising the fact that individual negative events can have multiple causes with different probabilities of occurrence, Steps 5 through 7 of the methodology were designed to address the multiple risks that may be associated with a single potential negative event.

The design of the Quality Risk Management worksheet was continuously modified during the testing phases of this methodology in order to help users understand the terminology and the headings used in the various parts of the worksheet. For example, explanatory comments and instructions were added into the various pages of the worksheet when testing work indicated that this was required. These additional text items were seen to improve the ease of use and the intuitiveness of the methodology, and helped users better understand the structure and intent of the various worksheet pages.

- In Step 9 of the worksheet, for example, the header "Action Items" was amended by adding explanatory text, to read: "Action Items - these could be actions to implement a control, or they could be a Qualification or Validation Exercise". This was because it was observed that some users of the methodology were forgetting to record Qualification or Validation exercises and related activities as action items that needed to be executed.

- In Step 6 of the worksheet, the meaning of the term "Detection Controls" was clarified with the addition of the following text: "List any controls currently in place which detect the negative event or its consequences after the negative event has occurred". This was to make it clear that detection controls were considered to be controls which operated after the negative event had occurred, and not earlier.

5.3.11 Strategy 11: Ensuring Clear and Simple rules are in place governing the use of this Quality Risk Management methodology

- ***At the outset of the Quality Risk Management exercise, the Team Leader is required to ensure that the team agrees on some simple & scientifically sound rules used by the Quality Risk Management methodology.***

5.3.11.1 Background Information on this Strategy:

There are several simple rules that govern this Quality Risk Management methodology, and it is important that the team is familiar with these prior to the start of any Quality Risk Management exercises using this methodology.

These rules are built into the design of the Quality Risk Management process and the documentation accompanying the methodology, but it is helpful to review those rules with the team in order to reduce the problems of subjectivity and uncertainty which may occur during Quality Risk Management exercises when its rules are not well understood.

Some examples of these rules are:

- That risk is the combination of the probability of occurrence of harm and the severity of that harm. In other words, Risk = Probability x Severity. This also implies that Risks and Risk Priority Numbers (based on P x S x D) are not the same, and should not be confused.

- That, in GMP environments, harm is considered to be damage to health, including the damage that can occur from loss of product quality or availability. The incorporation of product availability into this definition of harm is important, as otherwise, some risks which might lead to a loss of product availability but not quality may be seen as business-related only, and not as GMP-related, regardless of whether a GMP failure lead to the risk.

- That, even when a risk is deemed acceptable with current controls and when no new risk controls are required, qualification and validation requirements still need to be assessed and determined for those current controls, and the qualification and validation status of those controls needs to be identified and documented.

- That there may be some risks which cannot be eliminated or reduced to an acceptable level with current or realistic controls/resources, but which may be controlled to an acceptable level with improved detection or other measures.

- That, in GMP environments, a high detectability of a risk does not necessarily mean that the risk is eliminated or adequately controlled.

5.3.11.2 How the above Strategy was implemented in this Quality Risk Management methodology:

All of the above rules are built into the design of the Quality Risk Management process and the documentation accompanying the methodology, including the training materials that have been developed on the methodology.

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Chapter 6

Development of the Final Version of this Quality Risk Management methodology, and development of a practical Training Programme for the methodology

6.1 Introduction & Generation of the Final Version of the Methodology

All of the learnings identified during the testing of Version 3 of the methodology (as documented in Chapter 4) were compiled and evaluated. As a result, a number of design modifications were made to the methodology, and Version 4, the final version of the methodology, was the result of these modifications. The final version is presented in Volume 2, Part II, of this thesis.

The main modifications made to the methodology related to Step 4 of the Quality Risk Management process used by the methodology and to the content of the guidance presentation that had been developed for Version 3 of the methodology.

6.1.1 Modifications made to Step 4 of the Quality Risk Management process:

Step 4 of the Quality Risk Management process was modified to provide additional instruction and guidance for how this step of the process is to be executed. The changes in this regard mainly concerned the requirement to screen all of the potential negative events identified at Step 4 of the process in order to identify those that should be onward processed through the remaining steps of the Quality Risk Management process.

Information was also added to Step 4 of the process in relation to dealing with any potential negative events that were *not* selected for onward processing through the remaining steps of the Quality Risk Management process, and what should be recorded when this occurred.

The following is a summary of the revised version of Step 4 of the Quality Risk Management process:

Step 4: What might go wrong? - Identify & Screen Potential Negative Events:

- Review relevant documentation, records & data, and use brainstorming techniques to identify potential Negative Events for the Item under Study. (Note: Guidance on

brainstorming is provided in a Questions & Answers document which is provided with the methodology.)

- As this is a formal and rigorous Quality Risk Management methodology, only the highest priority/most important potential Negative Events should normally be selected for formal evaluation. To do this, the following approach may be used:
- Discuss and review all of the suggested potential negative events identified above, in terms of their expected consequences and their likelihood of occurrence.
- In this regard, the strength of evidence for the likelihood of occurrence of each potential negative event should be considered, and the severity of the consequences of each potential negative event should be discussed.
- The level of complexity associated with the each potential negative event, in terms of how the potential negative event might occur, should also be considered.
- At this stage, those potential negative events considered by the team to be the most important, in terms of their potential consequences and/or complexity, should be selected for formal onward processing in the remaining steps of the Quality Risk Management process. However, the likelihood of occurrence of each potential negative event should also be taken into account. If it is considered at Step 4 that a potential negative event has only a remote likelihood of occurring, then this potential negative event should not normally be selected for onward processing through the remaining steps of the process, unless there is good reason for doing so.
- The decisions made in relation to the above evaluations and considerations should be documented.
- In relation to dealing with any potential negative events not selected for onward processing through the remaining steps of the Quality Risk Management process, a record should be made of what these potential negative events were, and why they were not formally routed through the remaining steps of the process.
- The team may decide that any potential risk associated with these potential negative events should be managed in a less formal manner than this methodology requires, and information in this regard should be documented.
- Alternatively, the team may decide that these potential negative events should actually be processed through the remaining steps of this Quality Risk Management process at some later date, perhaps during the planned review of the exercise as part

of Periodic Review activities. This should be documented in Step 10 of the worksheet.

- Alternatively, the team may just recommend that these potential negative events be reviewed again at the next review of the exercise, to determine whether at that time they should be formally routed through the remaining steps of the process. Again, this should be documented in Step 10 of the worksheet.
- Lastly, there may be no need to give any more consideration to those potential negative events at all, following the above evaluation at Step 4 of their expected consequences and their likelihoods of occurrence. This should be documented.

6.1.2 Modifications made to the Guidance Presentation on the Quality Risk Management methodology:

The guidance presentation that had been developed for Version 3 of the methodology was designed to provide guidance on the execution of each step of the Quality Risk Management process. It had been structured in a Question and Answer (Q&A) type format. However, as a result of the learnings gained from the testing of Version 3 of the methodology, and following a review of the content of the existing guidance presentation, additional specific guidance was developed in the following key areas:

- How Step 4 of the Quality Risk Management process was to be completed with respect to the screening and selection of potential negative events for onward processing through the remaining steps of the process;

- How the methodology deals with disagreements of opinion during brainstorming and other team-based activities;

- How risk communication activities should be carried out, and what were the important factors to take into consideration when planning for risk communication activities;

- What items should trigger the Periodic Review element of the Quality Risk Management process.

In addition, extra and detailed guidance was developed on several general issues that were identified as being important to the use of this methodology, and this included guidance for dealing with a number of practical issues which arose during practical Quality Risk Management exercises. The areas in question related to the following activities:

- Dealing with common sources of subjectivity and uncertainty during Quality Risk Management exercises

- Dealing with the potential adverse influences of cognitive human heuristics in brainstorming and decision making

- How Strength of Evidence considerations should be taken into account when performing Quality Risk Management exercises

- The Definitions and Terminology used in this Quality Risk Management methodology

- The potential uses and limitations of this Quality Risk Management methodology

- General Issues in relation to GMP Controls

- Considerations in relation to Business versus GMP Risk issues

These modifications resulted in a Guidance presentation that is substantially more detailed and comprehensive than that provided with Version 3 of the methodology. It also is now structured into two main parts; Part I of the presentation addresses the above and other general areas of concern, and Part II provides the Q&A formatted guidance for each of the ten steps of the Quality Risk Management process.

The guidance presentation was designed to serve both as training material on this Quality Risk Management methodology, as well as step-by-step guidance that may be consulted when teams were actually performing Quality Risk Management exercises with this methodology. It was intended that trainees would review the content of Part 1 of the presentation as a prelude to receiving training on the actual components making up this methodology, such as the Quality Risk Management process and the accompanying Worksheet & Laminated Card. With respect to Part 2 of the presentation, it was intended that trainees would review the content of this part for guidance when starting their actual training on the ten step Quality Risk Management process and the accompanying Worksheet & Laminated Card.

To support the above Guidance presentation, a number of detailed Appendices were developed which provided further information and guidance in several key areas of concern when using this methodology. These areas had been identified as needing detailed, practical guidance during the testing and evaluation stages of this research. There were seven such Appendices developed for the Guidance presentation. These were:

Appendix 1 *- this provided detailed, practical guidance for carrying out team-based activities such as brainstorming during Quality Risk Management exercises;*

Appendix 2 *- this provided detailed, practical guidance for how disagreements and differences of opinion were to be dealt with during team-based activities such as brainstorming;*

Appendix 3 *- this provided detailed, practical guidance in relation to the potential adverse effects of human cognitive heuristics on Quality Risk Management activities and decision-making in general;*

Appendix 4 *- this provided detailed, practical guidance in relation to assessing the strength of evidence for opinions and judgements that have been given during Quality Risk Management exercises by team participants and subject matter experts;*

Appendix 5 *- this provided detailed, practical guidance on what information might be included when assembling comprehensive data on the Item under Study during a Quality Risk Management exercise;*

Appendix 6 *- this provided a practical GMP-related Case Study which was designed to help users understand several of the strategies that were developed during this research to overcome problems of subjectivity and uncertainty that were observed when identifying potential negative events and when performing Risk Assessment activities in general during this research. This Case Study also served as an example of how this Quality Risk Management methodology may be used in conjunction with other methodologies such as Fault Tree Analysis when identifying potential negative events and their likely causes;*

Appendix 7 *- this provided detailed, practical guidance on dealing with human error issues, and how to avoid situations in which human error may wrongly be identified as the cause of a potential negative event.*

6.1.3 Modifications made to the Quality Risk Management Worksheet

As a result of the learnings gained when working through the Case Studies that were developed to test and challenge Version 3 of the methodology, as discussed in Chapter 4, several minor modifications were made to the Quality Risk Management Worksheet and the Laminated Card components of the methodology.

The modifications to the Quality Risk Management Worksheet involved:

- *Inserting explanatory text into Steps 5, 6 & 7 of the worksheet in relation to the need to critically evaluate each GMP control before any Severity, Probability of Occurrence or Detection rating is assigned to a Potential Negative Event associated with that control;*

- *Inserting additional explanatory text into Step 1 of the worksheet in the section titled Process Map or Schematic in relation to the comprehensive data that is required to be assembled on the Item under Study at the beginning of the exercise*

- *Inserting a more explicit reference in Step 1 of the worksheet for the need to document all pertinent assumptions that are being made in relation to any part of this Quality Risk Management exercise*

- *Inserting an explicit reference in Step 4 of the worksheet for the need to consider any available information on near miss incidents in relation to the Item under Study*

- *Inserting an explicit reference in Step 4 of the worksheet for the need to screen all potential negative events in order to identify those potential negative events that should be onward processed through the remaining steps of the Quality Risk Management process. (The modified Quality Risk Management process as outlined above provides detailed information on how this screening activity should be performed.)*

- *Providing clarification text into Step 5 of the worksheet to explain that when there is more than one effect identified for a potential negative event, the Severity rating that is assigned to the effects of that potential negative event should reflect the most serious of those effects.*

- *Changing the text in the header of Step 10 of the Worksheet to read "What communications are required arising out of this QRM exercise, and when will this exercise be reviewed or revisited? This text was considered to more accurately reflect the purpose of this Step than the header for this Step used in Version 3 of the Worksheet.*

- *In Step 10 of the Worksheet, making reference to the fact that the Periodic Review activities of Step 10 represent a plan for the continuous improvement of the Quality Risk Management exercise.*

- *Inserting guidance into the section on Periodic Review activities in Step 10 of the Worksheet on what may be recorded in this section.*

- *Correcting a number of typographical errors that were present in Version 3 of the Worksheet*

6.1.4 Modifications made to the Quality Risk Management Laminated Card

The modifications made to the Laminated Card involved the correction of a number of typographical errors that were present in Version 3 of the Card, as well as clarifying the meaning of the Remote Probability of Occurrence rating shown on the card.

The latter change involved revising the wording for the Remote Probability of Occurrence Rating to read "The Pot. Neg. Event is Very Unlikely to Occur, or is Extremely Unlikely to Occur." (This was the original intent of the Remote Probability of Occurrence rating, but the latter part of this definition had inadvertently been omitted from the first version of the Laminated Card in error.)

6.1.5 Structure and Composition of the Final Version of this Quality Risk Management methodology

The final version of this Quality Risk Management methodology was structured around five main elements. The first four of these items have already been described in detail in earlier chapters of this thesis, and any changes made to those components in the generation of Version 4 of this methodology have been discussed above, in this chapter. The fifth element making up the final version of the methodology is described below.

The five elements making up the final version of this Quality Risk Management methodology are as follows:

Element 1 - A document stating each of the Principles underlying the design of this Quality Risk Management methodology and the design of the step-by-step process used by this methodology

As discussed in detail in Chapter 2, twelve such principles were defined at the beginning of the development of this methodology. These are set out in the above document, and a discussion on each is also included. The twelve principles were considered fundamental to the design and development of the methodology, right from the development of the initial basic version of the methodology, through to the development of the final version. The principles were tested during the rigorous testing and development work carried out on the methodology, and none of them had to be changed or modified during this work.

Importantly, these principles were not mere aspirational statements made at the beginning of this work; they were formally incorporated into all aspects of the design of the Quality Risk Management process and the associated explanatory guidance material that were developed for this methodology.

For example, when the consequences of a Potential Negative Event are being documented at Step 5 of the Quality Risk Management process, the guidance that accompanies Step 5 directs the team to consider both local and global effects in this regard. The so-called 'local' effects of the potential negative event include the effects it may have on the patient or animal (being administered the medicinal product), and on the healthcare professional involved in the use or administration of the product. Included in the 'global' effects category are the effects the potential negative event may have on the wider population group using the medicinal product or the service of concern in the Quality Risk Management exercise. The methodology also requires the team to always think of the potential patient (or animal) impact when assigning a Severity rating to those consequences of any potential negative event, and this is also reflected in the guidance material that was developed for Step 5 of the Quality Risk Management process.

The above aspects of the methodology reflect the content of Principle No. 8, which states: *The main stakeholders associated with the application of Quality Risk*

Management within GMP and Regulatory Compliance environments are patients and users of medicines, including healthcare professionals, as well as industry and regulators, and that, while the concerns of all involved stakeholders should be taken into account in any Quality Risk Management exercise, protection of the patient is of prime importance, and therefore, Quality Risk Management should ultimately link to the protection of the patient.

As discussed in Chapter 2, several of the twelve principles were based on the guidance and principles of ICH Q9. For example, Principles 2 and 8 of this methodology reflect the ICH Principle that the evaluation of the risk to quality should "ultimately link to the protection of the patient", and Principle 12 reflects the ICH Q9 Principle that the level of effort, formality and documentation of the quality risk management process "should be commensurate with the level of risk." (9)

It should be noted that ICH Q9 had not yet been finalised when this work was beginning (in early 2004), and thus, the ICH Q9 text was still in draft form at that time. The guidance presented by ICH Q9 on the principles of Quality Risk Management did change as the document was being developed, but the key points made in this regard remained constant through to the completion of ICH Q9. For example, a June 2004 draft of ICH Q9 stated a number of essential principles of Quality Risk Management, including the principles that the evaluation of the risk should ultimately link back to the potential risk to the patient, and that the extent of the risk management process should be commensurate with the level of risk associated with the [risk management] decision. Thus, it is evident that although the final ICH Q9 text was somewhat different than that drafted in June 2004, the key points in relation to the above Quality Risk Management principles remained the same.

Element 2 - A document providing an overview of the Ten Step Process used by this Quality Risk Management methodology

This sets out each of the steps in the Quality Risk Management process, and it defines the main work activities to be performed by the team during each of those steps. This document provides both instructional information and guidance to the Quality Risk

Management team when working through each step of the process. It is also designed to allow the team performing a particular Quality Risk Management exercise to check which step of the process the team is working on at any one time, and to review the activities required of that step.

Chapter 4 of this thesis provides a detailed description of the Quality Risk Management process, with the exception of Step 4 of the process, which, as discussed above in Section 6.1.1, was modified as a result of the learnings gained from the testing performed on Version 3 of the methodology.

ICH Q9 described 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. Thus, four key elements make up the ICH Q9 Quality Risk Management process - Risk Assessment, Risk Control, Risk Communication and Risk Review. (These are described in detail in Chapter 1.) A fifth element can be added to this list, which relates to the planning and other activities that need to be carried out prior to the actual execution of a Quality Risk Management exercise. These activities range from defining the problem and/or risk question at hand, to documenting any pertinent assumptions that may be important for the exercise at hand. They also include the assembly of background information or data on potential hazards, and the activities of setting up a Quality Risk Management team and selecting a team leader for the exercise at hand.

All of the above elements are addressed in the Quality Risk Management process developed for this methodology, and no modifications are required before the methodology may be used to execute the full Quality Risk Management process as defined by ICH Q9. For example, Steps 1 through 3 of the process address the planning and "setting-up" activities for the individual Quality Risk Management exercise; Sections 1 through 3 of the Worksheet provide the template for documenting the execution of those three steps, and the Training & User's Manual, (discussed below), presents detailed guidance on each of those steps, as well as guidance on key issues that may arise during their execution, such as what items should be assembled on the Item under Study in the exercise at hand, who should be the team for the exercise at hand, and why should the team be multi-disciplinary in nature.

The comprehensive nature of this Quality Risk Management process and its associated components contrast sharply with the design of many existing Quality Risk Management methodologies, which often tend to focus attention only on the Risk Assessment and Risk Control elements of the Quality Risk Management process, while neglecting to address in any meaningful way the other key elements, such as Risk Communication and Risk Review.

Element 3 - The Quality Risk Management Worksheet

As discussed in Chapter 4, the Quality Risk Management Worksheet is a highly structured, instructional template document, addressing each of the ten steps making up the Quality Risk Management process used by this methodology. It reflects all of the elements of Quality Risk Management as defined by ICH Q9, and no modification is required before it may be used to execute the full Quality Risk Management process as outlined in ICH Q9, and as set out in detail in this methodology.

The Worksheet was designed to both guide users through the ten-step Quality Risk Management process, and to document the Quality Risk Management exercise, right from defining the purpose and nature of the specific exercise at hand (Step 1), right through to planning for a formal review of the Quality Risk Management exercise at a later time-point (Step 10). It provides a high degree of instructional text for the team working through the Quality Risk Management exercise, and it uses explanatory section headings, wherever possible, to indicate the stage of the Quality Risk Management process that the team is working on at any one time.

The Worksheet thus presents a practical means of executing, step by step, the full ten step Quality Risk Management process provided by this methodology.

As discussed in detail in Chapters 2 through 4 of this thesis, the Worksheet was developed and optimised using a number of practical GMP-related Case Studies, workshops and problem-scenarios, and it was subjected to extensive user testing with industry and with academic validation and quality assurance groups.

Element 4 - The Laminated Card

This is used in conjunction with the Quality Risk Management Worksheet, particularly during Step 3 of this Quality Risk Management process, and also during Steps 5, 6 and 7. Its primary purpose is threefold:

1) to provide the various default definitions and levels for the Severity, Probability of Occurrence and Detection factors used by the methodology when characterising and estimating the risks associated with potential negative events;

2) to provide the Risk Table that is to be used by users of this methodology when assessing risks;

3) to facilitate a formal review of the default definitions for the Severity, Probability of Occurrence and Detection factors, so that those definitions may either be agreed by the Quality Risk Management team, or modified if required by the team.

Element 5 - A document providing an overview of the recommended strategy for the training of team leaders and users of this Quality Risk Management methodology

This document is in the form of a presentation. It sets out a practical and detailed training strategy for team leaders and users of the methodology, and specific required training activities are also defined.

This training strategy is discussed in detail below, in Section 6.2.3.2, which concerns the training requirements for users of this methodology.

6.1.6 The wide applicability of this Quality Risk Management methodology

The results generated by the various case studies and workshops used to test the methodology during its various stages of development demonstrated the wide applicability of the methodology across a broad range of areas within the GMP-regulated environment, as a solution for determining, on a risk basis, the scope and extent of validation and the likely impact of changes.

This was demonstrated by the successful application of the methodology across a broad spectrum of GMP areas and activities, for which, in each case, new qualification and/or validation requirements, or other additional actions, were identified that had not been identified prior to the execution of the Quality Risk Management exercise. In all cases, the qualification and/or validation requirements, and the other additional required actions, were directly related to the risks that had been identified during the Quality Risk Management exercises.

The GMP areas and activities to which the methodology was applied during this work included:

- *The final steps of the mixing and filling process for a Paracetamol Oral Suspension product at a finished medicinal product manufacturer:*

  - This involved the retrospective application of the Quality Risk Management methodology to the manufacturing process of concern.
  - It was performed in response to recurring deviations which had been experienced with the process in question.
  - Detailed information on this application of the methodology and its outcomes are provided in Chapter 2 of this thesis.

- *A film-coating process for a tablet product at a finished medicinal product manufacturer:*

- This involved the retrospective application of the methodology to the film-coating process of concern.
- Detailed information on this application of the methodology and its outcomes are provided in Chapter 2 of this thesis.

- *The early scale-up steps in a fermentation process that was used in the manufacture of a biotechnology-based antibody:*

  - This involved the retrospective application of the methodology to the fermentation process of concern.
  - Detailed information on this application of the methodology and its outcomes are provided in Chapter 2 of this thesis.

- *A proposed Change Control at a manufacturer of active substances:*

  - This involved the prospective application of the Quality Risk Management methodology to the concerned Change Control proposal.
  - The change in question related to a planned move from using a conical, centrifugal dryer to dry batches of the active substance to the use of a filter dryer, which was new to the plant in question.
  - Detailed information on this application of the methodology and its outcomes are provided in Chapter 2 of this thesis.

- *The material dispensing area at a manufacturer of solid oral dosage formulations:*

  - This involved the retrospective application of the methodology to the material dispensing area of concern.
  - In this case, the potential for cross contamination of active substances had been identified as a result of the open design of the dispensing area, and the Quality Risk management exercise had been performed as a result of these concerns.
  - Detailed information on this application of the methodology and its outcomes are provided in Chapter 3 of this thesis.

- *The potential use of a new critical product-contact material at a manufacturer of an intermediate investigational medicinal product:*

  - This involved the prospective application of the Quality Risk management methodology to the supplier approval procedure in question.
  - The material in question was to be used in the milling stages of a manufacturing process that made use of nano-milling technology in order to achieve the desired particle size profile of the intermediate investigational medicinal product.
  - Detailed information on this application of the methodology and its outcomes are provided in Chapter 3 of this thesis.

- *A proposed Change Control at a Quality Control laboratory used for the analysis of an active substance for Nickel content:*

  - This involved the prospective application of the Quality Risk Management methodology to the concerned Change Control proposal.
  - The change in question related to a proposed introduction of Inductively-Coupled Plasma/Mass Spectroscopy (ICP-MS) for the testing of an active substance which was manufactured via a new Nickel-catalysed synthetic route.
  - This Change Control also proposed the use of ICP-MS for the analysis of another active substance as well as water samples that were analysed at the laboratory in question.
  - Detailed information on this application of the methodology and its outcomes are provided in Chapter 4 of this thesis.

- *The product distribution and recall system in place at a manufacturer of finished medicinal products:*

  - This involved the retrospective application of the Quality Risk Management methodology to the concerned product distribution and recall system.
  - The manufacturer in question was unusual in that it shipped its products directly to hospitals and patients' homes without making use of any wholesaler company.
  - Detailed information on this application of the methodology and its outcomes are provided in Chapter 4 of this thesis.

In each of the above cases, including the change control proposals, GMP controls were identified that were important in either maintaining risks at certain levels, or in achieving a reduction in risks. A critical evaluation of those controls in Step 8 of the Quality Risk Management process led to the determination of critical process parameters and their associated specifications/limits, or to the identification of other required outcomes for controls, in situations where it was not possible to determine critical process parameters for the control at hand.

This resulted in the formal assessment of the qualification and/or validation requirements for each risk-based control. In some cases, GMP controls that were required to address an identified risk were personnel or training-related, and the methodology proved capable of dealing with the qualification requirements for those personnel competency and training-related controls. As the development of the methodology progressed, the qualification and/or validation *status* of each risk-mitigating control was also identified.

In this way, the methodology served as a practical solution for determining, on a risk basis, the scope and extent of validation, and the likely impact of changes. It successfully identified risk-based qualification and/or validation items that were required to address the risks that had been identified during application of the Quality Risk Management process to the Item under Study.

In addition to the above Case Study and Workshop testing activities, some specific and important aspects of the methodology, such as the way in which the methodology deals with risk detection issues, and the way in which GMP controls are classified during Steps 5 through 7 of the Quality Risk Management process, were further studied. This was in order to determine how well those aspects of the methodology applied to a range of different situations, problems and scenarios.

The situations, problems and scenarios investigated were as follows:

- The potential for a packaging process to fail to ensure that a Patient Information Leaflet is inserted into every pack of a medicinal product packaged on that packaging line. The medicinal product in question was used to treat moderate to severe depression;

- A recurring problem of the presence of glass particles in filled and sealed vials of a parenteral medicinal product;

- A deviation involving the failure to record room differential pressures during the aseptic processing of a batch of a parenteral medicinal product;

- An autoclave pressure chart recorder failure during the sterilization of a load of filters for use in the aseptic filtration and filling of a solution in an aseptic processing facility;

- A failure to correctly read the pH of a solution prior to performing an important pH-dependent extraction step during the processing of a batch of an active pharmaceutical ingredient.

- An error during the labelling of blood component collection bags at a Blood Establishment, resulting in an incorrect Unit ID Number (e.g. a bar code identifier for the bag), being labelled on the bag in question, and the loss of traceability of the bag to the donor of the blood;

- A particulate contamination issue affecting a batch of platelet aphoresis units at a manufacturer of such products at a Tissue Establishment;

The above situations, problems and scenarios were studied by the author during the various testing and development work activities performed on the Quality Risk Management methodology. A number of these were also referred to during several of the workshops run on the methodology by the author, (e.g. the workshops referred to in Chapters 2 and 4 of this thesis), and in a number of presentations given by the author on the methodology, such as those given at a PIC/S Blood & Tissues Expert Circle Meeting of October 3rd, 2007 in Dublin (137), and at a PharmaChemical Ireland/PDA/ISPE Quality by Innovation conference in Cork, on November 14th, 2007 (138).

In all of the above situations, problems and scenarios, it was concluded that the methodology performed precisely as intended. This was in relation to how risk detection issues were dealt with, and in relation to how GMP controls that were pertinent to the failure or problem at hand were classified. (This latter area reflected the role played by the GMP controls in determining the severity, probability of occurrence or detectability of the particular failure mode or potential negative event at hand.)

During the application of this methodology to Change Control proposals, it was observed during this research that different schools of thought existed on whether formal Quality Risk Management approaches such as this one add value to existing Change Control programmes at pharmaceutical companies. Differing views were put forward by individuals encountered by the author during this research work on how Quality Risk Management, in general, fits in with pharmaceutical Change Control activities.

For example, during two of the workshops run using Version 3 of this methodology, as discussed in Chapter 4 of this thesis, some participants in the workshops expressed the view that *Change Control* represents a Risk Assessment methodology in itself, and as a result, there was no need for any additional Quality Risk Management-type methodology to be used in relation to proposed changes. Others participants in those

same workshops expressed the opposite opinion, and held that formal Quality Risk Management activities should be quite separate from any specific Change Control procedure that may be in place, and that Quality Risk Management should be a *stand-alone* item within a company's Quality Management System.

The author has studied this area carefully during this research work, and has found that a well designed Change Control programme can be considered to be a Quality Risk Management approach in its own right. This represents, however, a somewhat informal application of Quality Risk Management. This is because, while Change Control procedures, by definition, recognise the fact that proposed changes, if implemented without formal procedural oversight, may pose risks to product quality, patient or animal safety, the company's GMP compliance status, etc, they do not usually provide the independence of thought and level of rigor required for more formal Quality Risk Management work. Also, such procedures usually do not contain all of the required elements of the full Quality Risk Management process, as defined in ICH Q9.

When formal Quality Risk Management work was separated from routine Change Control work, as was the case in the Change Control-related case studies and workshops documented in this work, this research found that there was more of an opportunity to take an objective step back from the proposed change, so that a more comprehensive and rigorous evaluation of the potential risks presented by the proposed change could be made. This was confirmed in each of the Change Control-related case studies and workshops that were developed and run using this methodology, where risks were identified during the Quality Risk Management exercise that had not been identified prior to execution of the exercise.

In summary, the findings of the above work demonstrated that the Quality Risk Management methodology developed here is applicable to a wide range of products, (including active pharmaceutical ingredients, finished medicinal products, and investigational medicinal products), across a range of materials and dosage forms (e.g. solid powders, tablets, oral suspensions, parenteral solutions) and to a diverse range of different GMP-related activities, such as quality control testing, packaging and labelling activities, supplier approval and product recall-related activities. In addition, both

retrospective and prospective applications were easily facilitated by the methodology, as were formal Change Control proposals.

6.1.7 How the final version of this methodology draws upon, and contrasts with, several existing Quality Risk Management methodologies and approaches

This methodology draws upon some of the useful features of existing Quality Risk Management methodologies and approaches that are currently in use in the GMP environment. It also differs from these methodologies and approaches in many important respects. The following sections present a detailed discussion in this regard.

6.1.7.1 With respect to the FMEA & FMECA-based Quality Risk Management approaches:

This methodology draws upon some of the useful features of the FMEA (Failure Mode & Effects Analysis) & FMECA (Failure Mode, Effects and Criticality Analysis)-based Quality Risk Management approaches, (46, 47, 51), in that it recognises the value in assigning Probability of Occurrence, Severity and Detection ratings during Risk Assessment activities, and in re-assessing those ratings during Risk Control activities.

This methodology also recognises the value in breaking down the item under study into manageable components for individual assessment; it recognises that all problems are not the same, and that a formal prioritisation of risks and their related risk control actions should be carried out.

However, this approach differs markedly from FMEA or FMECA-based methodologies in several important ways. For example, unlike the FMEA and FMECA-based methodologies, before any risks associated with a potential negative event are formally assessed via this methodology, the team performing the exercise is required to formally identify, document and critically evaluate any and all GMP controls that have the potential to influence the severity of the effects of the potential negative event, the probability of occurrence of its causes, or its detectability. Only then may Severity, Probability of Occurrence and Detection ratings be assigned to the potential negative

event at hand. This critical evaluation of GMP controls applies not only to currently-in-place controls, but also to any new or improved GMP controls that are proposed during the Quality Risk Management exercise.

Additionally, this methodology formally requires the team performing the Quality Risk Management exercise to determine the qualification and/or validation status of, and the related qualification and/or validation requirements for, all of the GMP controls that were identified as being important for each potential negative event identified. This means that even when a risk is deemed acceptable with currently-in-place GMP controls, the qualification and/or validation requirements for those existing controls, and the status of such, must be assessed and documented. This is not a feature of FMEA or FMECA-based approaches.

The approach developed here formally prioritises risks and any required qualification and/or validation-related activities on the basis of the estimated magnitude of each risk, not on the basis of an estimated 'Risk Priority Number' for any risk, as in FMEA or FMECA-based approaches. Risk Priority Numbers are not calculated when using this methodology, as they do not represent an estimate of the magnitude of a risk.

One reason for this is the way in which this methodology handles risk detection issues – this occurs in a markedly different way than in FMEA or FMECA-based methodologies. Here, detection controls are considered and evaluated after the risk has been estimated, not before, and a formal and critical evaluation of detection controls is required in order to determine whether those controls actually give assurance that the risk in question is adequately controlled & that no further controls are required. This is regardless of the magnitude of the detection rating assigned to the detection-related controls for the potential negative event in question. Thus, in this approach, detection ratings are purposely given decreased prominence during the overall Risk Assessment process.

One advantage of this approach to detection issues is that, it serves to separate out detection-based controls from other GMP controls, so that it can be determined how reliant the risk mitigating and control strategies are on detection-based controls. This is useful to know in GMP applications, as GMP is more concerned with the *assurance of*

quality via the design of the manufacturing process and its related controls, than with using detection-type controls to present evidence of quality.

Also, in contrast to FMEA and FMECA-based methodologies, '*Failure Mode*' terminology is not used here. While the term *Failure Mode* was in fact used in the early versions of this Quality Risk Management methodology, in several of the workshops run on this methodology, it was (somewhat unexpectedly) observed that this term was not intuitively easy for some workshop participants to understand. In some cases, confusion was observed between what was a Failure Mode and what its potential effects were. As explained in Chapter 2 of this thesis, this adversely impacted upon the outcomes of the Quality Risk Management exercises in question, particularly in relation to the GMP controls that were identified during the exercises as being risk-mitigating.

To address such problems, the *Failure Mode* terminology was eventually discarded in favour of the term 'Potential Negative Event'. The term *Potential Negative Event* is used to denote 'what can go wrong' with, or in, the Item under Study in the Quality Risk Management exercise. This term was immediately preferred among workshop participants when introduced, being intuitively somewhat easier to understand than the term 'Failure Mode'. In addition, the Potential Negative Event terminology is applicable to a wider range of activities and areas, and is not confined to FMEA-type applications. In this methodology, a Potential Negative Event can be a single event, or a number of individual occurrences leading to a negative outcome. Risks arising from Potential Negative Events are estimated, assessed and controlled in Steps 5-7 of the Quality Risk Management process. Recognising the fact that individual Potential Negative Events can have multiple causes with different probabilities of occurrence, the methodology is designed via Steps 5 through 7 of the Quality Risk Management process to address the multiple risks that may be associated with a single Potential Negative Event.

Lastly, in contrast to FMEA and FMECA-based methodologies, this approach formally incorporates Risk Communication requirements into the Quality Risk Management process, as well as formal Periodic Review requirements for the Quality Risk Management exercise. These activities are often not built into the design of FMEA and

FMECA-based applications, and as a result, those methodologies often provide little or no guidance on how those important activities are to be carried out.

6.1.7.2 With respect to the HACCP approach to Quality Risk Management:

This methodology also draws upon some of the features of the Hazard Analysis and Critical Control Points (*HACCP*) Quality Risk Management approach, (48-49), in that it recognises the value of preventative measures over detection-related measures, and the value in determining critical control points, their related limits & target levels. HACCP also provides a comprehensive and documented approach for practical Risk Management exercises, which is useful.

However, in contrast to this approach, HACCP-based applications do not normally offer a clear, formal process for characterising or differentiating, (by either qualitative or quantitative means), the risks posed by a potential hazard, and the HACCP requirement to pre-define corrective actions for situations when Critical Control Point limits have been exceeded is not used here.

In contrast, this methodology provides a formal means of assessing individual risks, and it focusses on identifying and implementing GMP control measures which give assurance, via qualification and validation activities, that such risks are either reduced to an acceptable level, or controlled to an acceptable level.

6.1.7.3 With respect to the ISPE's Impact Assessment and GAMP4 approaches to Quality Risk Management:

This methodology recognises the value and importance of other useful Quality Risk Management approaches and official guidance documents in this field. These include the ISPE's Impact Assessment method for determining component criticality and related commissioning and qualification requirements for equipment and facilities (67), the Risk Assessment methodology for the validation of computerised systems as described in the ISPE's by GAMP4 publication (55), and the guidance on analytical

method validation as presented by ICH in its method validation Q2(R1) guideline of November 2005 (120).

Importantly, the methodology developed here was not designed to replace the above approaches in their specific areas of application, and in fact, it complements their use in many respects. One example of this is that, when one is using this methodology to determine the scope and extent of validation (and qualification) required for a particular equipment train or manufacturing process, the ISPE's Impact Assessment process can be helpful in determining where efforts with this methodology should be directed, as some of the critical components in the Item under Study will have already been identified using the ISPE's approach.

The Quality Risk Management methodology developed here draws upon some of the features of ISPE's approach. For example, it recognises the value in using structured and systematic techniques to determine critical components of systems on an 'impact' basis, especially with respect to product quality. It also recognises the value in focussing qualification activities on those critical components.

However, the approach described here goes beyond component criticality identification and assessments of impact; it provides for a full Risk Assessment process to be carried out on potential hazards, and this includes the consideration of the risks presented when equipment and system faults occur. This is not normally a feature of the ISPE's approach. In addition, unlike the ISPE's approach, formal Risk Control, Risk Communication and Periodic Review activities are built into the design of the Quality Risk Management methodology developed here.

With respect to the Risk Assessment process offered in the ISPE's *GAMP4* publication (55), the methodology developed here draws upon some useful aspects of the GAMP approach. It recognises, for example, the value in estimating risks only on the basis of likelihood of occurrence and severity considerations, not on detection factors, and the value in using the Risk Assessment process to help focus validation activities and to assess change control proposals. Also, the GAMP Risk Assessment process considers the complexity and degree of customisation of the Item under Study when determining

how much rigor to apply during the Quality Risk Management process, and this is a feature of the methodology developed here as well.

However, and importantly, the methodology developed here deals with risk detection quite differently, as it does not allow users to automatically assign risk priorities simply on the basis of detection ratings.

6.2 Training Programme for this Quality Risk Management methodology

It is well documented in the literature that people can be inherently poor at assessing risks (50, 87, 89, 92, 96), and so the value of training on Quality risk management should not be underestimated.

Throughout this research, training was identified as an area which was vital in ensuring the correct use of this Quality Risk Management methodology. For example, during the various workshops and the Case Study exercises run with the methodology, a number of practical difficulties and problems were encountered when explaining and using the methodology with prospective users. These problem issues can be grouped into two broad categories – General Quality Risk Management issues, and issues specific to this particular Quality Risk Management methodology.

6.2.1 General Quality Risk Management Training Issues

It was evident early in the development of this methodology that Risk and Quality Risk Management were concepts that were sometimes not well understood by many prospective users of Quality Risk Management methodologies.

In some cases, during the workshops run with this methodology, it was common to observe a misunderstanding in some workshop participants about how risks should be estimated and expressed, either qualitatively or quantitatively. For example, often a Risk Priority Number, (based on the combination of the three factors, probability of occurrence, severity and detection), was considered to be the best way to express the

magnitude of a risk associated with a particular Failure Mode. This was the case even when users fully accepted the definition of risk given in ICH Q9, which involves only two of those factors, the probability of occurrence of harm and the severity of that harm.

In relation to Quality Risk Management as a general concept, often there was a poor understanding of what activities make up the Quality Risk Management process, and Quality Risk Management-related activities such as Risk Communication and Risk Review were often largely underdeveloped and poorly understood.

6.2.2 Specific training issues for this particular Quality Risk Management methodology

In relation to the difficulties and issues encountered which were specific to this Quality Risk Management methodology, one important issue related to the way in which GMP controls are dealt with in the methodology. This was particularly the case during the early stages of this research, when the early versions of the methodology lacked detailed guidance in this area.

This methodology requires a formal and rigorous treatment of GMP controls, from the initial critical evaluation and classification of current GMP controls during Step 5 & 6 of the Quality Risk Management process, to the incorporation of new or improved GMP controls during Risk Control activities, at Step 7 of the process. In addition, at Step 8, there is a requirement to determine not only critical process parameters and their specifications/limits for GMP controls, but also to determine the required outcomes and acceptance criteria for any controls that are not readily described in terms of critical process parameters.

Another issue related to the area of *business versus GMP risk*, and how they differed. During the testing of this methodology with various stakeholder groups, it was sometimes observed that there was a belief among some individuals that, when GMP-based risks potentially affected production but not product quality, these were *business-related* risks, and were considered to be outside the remit of GMP control. Such individuals were of the opinion that risks of this nature should not be subjected to any

GMP-related Quality Risk Management activities. This researcher was and is of the opinion that such an approach would be contrary to the principle and guidance presented in ICH Q9, where risk is defined in terms of harm, and where harm may not just result from a loss of product quality, but also from the loss of product availability.

Another issue that arose during the testing and development of this methodology was the fact that some features of the methodology are not immediately obvious, and require explanation. Two examples of this are 1) the process for the identification of Potential Negative Events, and 2) what to do when conflicts arise during brainstorming and other team-based activities. The use of examples and practical Case Studies was necessary to explain and demonstrate how the methodology deals with these aspects.

6.2.3 The development of specific training strategies and training materials

In response to the above and other observations, specific training strategies and materials were developed during this research work in order to address the issues and difficulties identified. This resulted in the development of a comprehensive package of training documentation and materials on this Quality Risk Management methodology.

These training materials were designed not only for trainers and potential users of the methodology, but also for both potential Team Leaders and facilitators of Quality Risk Management exercises.

All of the training materials have been assembled and structured in the form of a *Training & User's Manual* for this methodology. This was designed to provide not only materials for use during training activities on the methodology, but also, materials and guidance for use during the execution of actual Quality Risk Management exercises, for each step of the ten-step process.

6.2.3.1 The Training & User's Manual

As mentioned above, the *Training & User's Manual* is a package of documents designed to be used as training materials and resources for both trainers and trainees on the methodology. It also provides detailed and practical guidance materials for use during the execution of actual Quality Risk Management exercises.

The Training & User's Manual is intended to be given to all trainees at the start of their training, and it should always be available during actual Quality Risk Management exercises. It contains five components, as outlined below:

Component 1: A copy of an Introductory Presentation on the methodology:

This presentation provides:

- A general introduction to this Quality Risk Management methodology and its key concepts;
- Background information on the development of this methodology, and information on some of the early key findings made during its development;
- The structure of the methodology, its uses and key features;
- The scope and uses of the methodology, and its expected outputs;
- The limitations of the methodology, as well as some advantages in using the methodology;
- A high-level overview of the Ten Steps making up the Quality Risk Management process used by the methodology;
- An overview of the principles upon which this Quality Risk Management methodology is based;
- A high-level overview of Quality Risk Management in general, including some of its basic concepts and definitions;
- An outline of the training requirements for this methodology.

Component 2: A detailed Guidance Presentation on the methodology

As discussed above, this presentation provides both general guidance on the methodology, as well as specific and detailed guidance on key activities and issues which may arise when working through each step of the Quality Risk management process.

The presentation is structured into two parts, as follows:

- Part 1 provides guidance on a number of practical issues which can arise during Quality Risk Management exercises. This guidance should be considered by the Quality Risk Management team before using this Quality Risk Management methodology.

- Part 2 of the presentation provides practical answers and specific guidance in relation to common questions which may arise when executing the various steps of the ten step Quality Risk Management process. For simplicity and ease of use, Part 2 is structured mainly in a Questions and Answers (Q&A) type format.

The presentation was designed to serve both as training material on this methodology, as well as step-by-step guidance to be consulted when actually using this Quality Risk Management methodology in specific Quality Risk Management. It was primarily designed as a resource for training potential team leaders of Quality Risk Management exercises; it is not specifically designed for other team members. In this regard, it is recommended that trainees should review the content of Part 1 of the presentation for general guidance on some key issues which are important before starting to train on the actual Worksheet component of the methodology. Trainees should review the content of Part 2 of the presentation for guidance when starting to train on the ten step Quality Risk Management process and the accompanying Worksheet & Laminated Card.

When performing a Quality Risk Management exercise with this methodology, each participant of the team should have a paper (or electronic) copy of the Guidance Presentation for reference, and when at a particular Step of the process, the relevant slides for that Step should be consulted for guidance, where necessary.

Supplementing this Guidance Presentation are a number of detailed *Appendices* which provide further information and practical guidance in several key areas of concern that arose when using this methodology during its testing and evaluation phases. These areas had been identified as requiring detailed, practical guidance, over and above that which had already been developed. There were seven such Appendices developed for the Guidance Presentation. These are as follows:

- Appendix 1 provides detailed, practical guidance for carrying out team-based activities such as brainstorming during Quality Risk Management exercises;

- Appendix 2 provides detailed, practical guidance for how disagreements and differences of opinion are to be dealt with during team-based activities such as brainstorming;

- Appendix 3 provides detailed, practical guidance in relation to the potential adverse effects of human cognitive heuristics on Quality Risk Management activities and on decision-making in general;

- Appendix 4 provides detailed, practical guidance in relation to assessing the strength of evidence for opinions and judgements that have been given during Quality Risk Management exercises by team participants and subject matter experts;

- Appendix 5 provides detailed, practical guidance on what information might be included when assembling comprehensive data on the *Item under Study* during a Quality Risk Management exercise;

- Appendix 6 presents a practical GMP-related Case Study which was designed to help users understand several of the strategies that were developed during this research to overcome problems of subjectivity and uncertainty that were observed when identifying potential negative events and when performing Risk Assessment activities in general during this research. This Case Study also served as an example of how this Quality Risk Management methodology may be used in conjunction with other methodologies, such as Fault Tree Analysis, when identifying potential negative events and their likely causes;

- Appendix 7 provides detailed, practical guidance on dealing with human error issues, and how to avoid situations in which human error may wrongly be identified as the cause of a potential negative event.

Component 3: A copy of a partially completed and fully completed Case Study on the methodology which involves an area not in any way related to GMP

A key part of the Training Programme on this methodology is the requirement for trainees to review a series of practical Case Studies that were developed using this methodology. While the majority of these Case Studies are GMP-related and are based on real-life GMP situations and issues, one of the Case Studies is not in any way related to GMP. That particular Case Study makes up this component of the Training & User's Manual.

The Case Study in question relates to the application of this Quality Risk Management methodology to a Wedding. It is a humorous, simple exercise, designed to put trainees at ease at the start of their training. This is important, given the vigorous and formal nature of the Quality Risk Management methodology. The intention here is that the trainees work through a partially completed version of the Wedding Case Study that is provided in this section of the Training & User's Manual, in order to complete the exercise and to learn how the methodology works in practice. This allows the trainees to become familiar with the main components of the methodology, (e.g. the Quality Risk Management Worksheet and the Laminated Card), as well as the ten-step process used by the methodology, before applying it to GMP problems and areas.

This approach allows trainees to explore and resolve any practical issues or difficulties that they may have with the methodology in a non-technical setting, before moving on to GMP-related applications of the methodology. At the end of this Case Study, the team evaluates their results obtained from their completion of the Case Study, and reference is made to a fully completed version of the Case Study which is provided in the same Training & User's Manual.

This Case Study facilitates the initial training on the methodology in a manner that is non-technical from a GMP perspective. It allows trainees to focus only on the methodology and how it is used, not on any GMP issues. This research found that using this type of approach greatly facilitates the training process. It was observed that it was a mistake to start with GMP-based case studies when users were being initially trained on this methodology. This was because trainees often focussed on the GMP issues rather than learning how the use the actual methodology. Therefore, it was considered useful to have a Case Study for in use training activities that was not related to any GMP area or activity, which demonstrated how the methodology works at a practical, everyday level, before moving on to GMP examples.

Component 4: A series of practical and completed real-life GMP-related Case Studies on the methodology

This section of the Training & User's Manual contains a series of practical and completed real-life GMP-related Case Studies which show, in practical terms, how this methodology may be used, and what the expected outputs of the methodology are when it is applied to specific GMP and GMP-related activities.

The inclusion of GMP-related Case Studies in the Training & User's Manual was considered important, because it allows potential users of the methodology to move beyond the conceptual, and to learn how to apply the methodology in the field that is of specific relevance to their area of work. It is for this reason that the following series of practical, GMP-related case studies are included in this Training & User's Manual.

- Case Study: The retrospective application of this Quality Risk Management methodology to a Paracetamol Oral Suspension Mixing & Filling Process at a Finished Product Manufacturer

- Case Study: The retrospective application of this Quality Risk Management methodology to a Material Dispensing Area at a Finished Product Manufacturer

- Case Study: The prospective application of this Quality Risk Management methodology to a proposed Change Control involving the introduction of ICP-MS analysis at an API manufacturer

- Case Study: The retrospective application of this Quality Risk Management methodology to a Product Recall Procedure at a Finished Product Manufacturer which supplies products directly to hospitals

- Case Study: The prospective application of this Quality Risk Management methodology to a proposed Change Control at an investigational Medicinal Product manufacturer, to introduce a new critical product contact material during a milling process

- Case Study: The retrospective application of this Quality Risk Management methodology to a GMP-related activity (A Quality Defect investigation programme run by a GMP Inspectorate at an EU Competent Authority)

Component 5: Copies of three peer-reviewed research papers describing this Quality Risk Management methodology

These papers provide general and detailed information on this specific Quality Risk Management methodology.

In the first two papers, the Quality Risk Management methodology is described, and the principles underlying its design are discussed. The design criteria used for development of the Quality Risk Management methodology are outlined, and the ten-step process used by the methodology is described. The scope and structure of the methodology, and some of its key features, are described, and some of the limitations of this methodology are outlined.

The third paper in this series describes some of the strategies built into the design of this Quality Risk Management methodology to address the problems of subjectivity and uncertainty that can be encountered during Quality Risk Management activities. These

are practical, easy to implement strategies that have been found to be useful during the development of this Quality Risk Management methodology.
The reference citations for these papers are as follows:

- *O'Donnell, K., Greene, A., A Risk Management solution designed to facilitate risk-based Qualification, Validation & Change Control activities within GMP and Pharmaceutical Regulatory Compliance Environments in the EU, Part I, Journal of GXP Compliance, Vol. 10, No. 4, July 2006*

- *O'Donnell, K., Greene, A., A Risk Management solution designed to facilitate risk-based Qualification, Validation & Change Control activities within GMP and Pharmaceutical Regulatory Compliance Environments in the EU, Part II, Journal of GXP Compliance, Vol. 10, No. 4, July 2006*

- *O'Donnell, K., Greene, A., Failure Modes - Simple Strategies for improving qualitative Quality Risk Management exercises during Qualification, Validation and Change Control Activities, Journal of Validation Technology, Vol. 13, No. 2, February 2007*

6.2.3.2 The Recommended Training Strategy for Users of this Methodology

A number of discrete, structured training activities were developed as part of the recommended training strategy on this Quality Risk Management methodology. These are described below.

The individual training activities should be carried out in the order in which they are presented below, taking into account the following considerations.

- It is appropriate that each company or organisation planning to use this Quality Risk Management methodology would develop its own specific training programme for potential users of this methodology. The type of training programme required, and the time to be spent on training activities, will depend on several factors, including, the purpose of the training (whether it is Team Leader training or Team Participant

training), the number of Case Studies to be covered during the training, and the degree of familiarity that the trainees already have on Quality Risk Management activities generally. The extent of training required should thus be determined on a case by case basis, taking these factors into account.

- Team leaders should generally receive much more detailed and technically-advanced training than non-Team leaders. This is because Team Leaders are generally expected to be the members of the Quality Risk Management team with the highest level of technical knowledge and competency on the methodology, and because it is not necessary for all team members to attain this level of competency. For individuals undergoing training to become Team Leaders of Quality Risk Management exercises, it is intended that the trainees would undergo all of the training activities (A through G) listed below. The number of Case Studies covered during the training should include one non-GMP related Case Study, and at least three GMP-related Case Studies. For this level of training, the expected total duration of the training activities would be approx. 30 hours, (about four working days). For each additional case study, approximately 2.5 hours should be added.

- For those individuals undergoing training to become *Team Participants*, but not Team Leaders, in Quality Risk Management exercises, it is intended that the trainees would undergo all of the activities listed below except Activity G. In addition, the time spent on each training activity may be considerably shorter than that for team leader training. For this level of training, the expected total duration of the training activities would be approx. 11 hours (about one and a half working days).

- Whether the specific recommended training activities outlined below are used or not in the company performing the Quality Risk Management training, it is important that the contents of the Training & User's Manual provided with the methodology are incorporated into any training programme developed on this Quality Risk Management methodology.

The following are the recommended training activities to be carried out when performing training on this Quality Risk Management methodology:

Recommended Training Activity A (Expected Duration: 2 hours)

Before the formal training begins on this Quality Risk Management methodology, trainees should be requested to read and familiarise themselves with the contents of ICH Q9.

Confirmation of this self-training on ICH Q9 should be documented as a pre-requisite for the training on this specific Quality Risk Management methodology

Any issues which were encountered during this self-training on ICH Q9 should be resolved by the Trainer of this Quality Risk Management methodology at the outset of training. (Expected Duration: 2 hours)

Recommended Training Activity B (Expected Duration: 1.5 hours)

The Introductory Presentation on the methodology should be presented to the trainees. Any issues or questions that arise during this presentation should be discussed and resolved by the trainer during or following the presentation.

Recommended Training Activity C (Expected Duration: 3 hours)

The trainees should be introduced to the following components of the methodology:

- The twelve principles underlying this Quality Risk Management methodology;
- The outline of each of the ten steps of the Quality Risk Management process used by this methodology;
- The Worksheet used by this methodology;
- The Laminated Card used by this methodology.

Any issues or questions that arise during this activity should be discussed and resolved by the trainer.

Recommended Training Activity D (Expected Duration: 2 hours)

A brief workshop should now be run with the trainees on the Case Study provided in the Training & User's Manual that involves the application of this Quality Risk Management methodology to an area not in any way related to GMP. (This is the wedding-related Case Study, contained in Component 3 of the Training & User's manual.)

This Case Study was designed to allow trainees to focus only on the methodology and how it is used, not on any GMP issues, during this training activity. It is intended to serve as a humorous, simple Quality Risk Management exercise, to put people at ease at the start of their training.

The trainees and the trainer should work through the partially completed version of the Case Study provided in Component 3 of the Training & User's Manual, in order to complete the exercise and to learn how the methodology works in practice. This Case Study is designed to enable trainees to become familiar with the main components of the methodology (e.g. the Quality Risk Management Worksheet, Laminate Card) and also the ten-step process used by the methodology, before applying it to GMP areas and related problems.

This simple Case Study allows the trainees to explore and resolve any practical issues or difficulties which may be encountered in a non-technical setting, before moving on to GMP-related applications with the methodology.

At the end of this training activity, the team should evaluate their results from completing the Case Study, with reference to a fully completed version of the Case Study which is also provided in Component 3 of the Training & User's Manual, for reference.

Recommended Training Activity E (Expected Duration:

- ***11 hours for Team Leaders***
- ***3.5 hours for Team Participants***

The Guidance Presentation on the methodology should be presented to the trainees. This contains comprehensive and technical guidance on specific features and aspects of the methodology, and as discussed above, it has seven detailed appendices.

Any issues or questions should be discussed and resolved during the presentation. A copy of the blank Quality Risk Management Worksheet and the Laminated Card are required when going through this presentation. Note: this training may be spread over two days (i.e. via two half-day sessions.)

This Guidance presentation, together with its appendices, is intended mainly for use when training potential Team Leaders. Team Participants should, however, be introduced to the presentation, to the guidance that it contains, and to how it is structured. The Team Participants do not need to be trained in the full content of the presentation or its appendices; rather, they should be able to make use of the presentation and its appendices during actual Quality Risk Management exercises, when questions or problems arise that require guidance.

Recommended Training Activity F (Expected Duration:* 2.5 hours per Case Study*)

The trainer should review in detail with the trainees one or more of the GMP-related Case Studies provided in the Training & User's Manual. This is in order for potential users of the methodology to understand the practicalities of applying this Quality Risk Management methodology to specific GMP areas, activities and problems. Any issues or questions should be discussed and resolved during this review.

It is imperative that there is interaction and discussion among the group during this review of the Case Studies. The trainer should frequently refer the trainees to the aforementioned Guidance Presentation, to demonstrate how the specific guidance provided in that presentation can facilitate the correct use of this methodology.

Potential Team Leaders should be trained on at least three GMP-related Case Studies. Team Participants should be trained on at least one GMP-related Case Study.

Recommended Training Activity G (Expected Duration:* 3 hours*)

The trainer should request the trainees to review, in their own time, the three peer-reviewed research papers contained in Component 5 of the Training & User's Manual. These papers describe this Quality Risk Management methodology, and they are useful for obtaining general and detailed information on this methodology, and on how the methodology addresses issues relating to the subjectivity and uncertainty in Quality Risk Management.

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Chapter 7

Risk Management in the Aeronautics and Nuclear Power generation industries, and a comparison of the approaches used in those industries with the Quality Risk Management approach developed in this research work

7.1 Introduction

In order to further critically evaluate the approach to Quality Risk Management developed in this research work, it was decided to study how Risk Management has been used in other industries, and to compare this approach with the Risk Management approaches used in two non-pharmaceutical industries that can be considered mature in their use and application of Risk Management methodologies. This allowed a broad assessment of the methodology developed here to be carried out, without being constrained by GMP-related considerations and issues.

The intent of this exercise was to benchmark this Quality Risk Management methodology against what may be considered to be *best practice* in other, non-GMP related areas. This was so that a rounded assessment of this methodology could be made. In this regard, the aeronautics industry, as represented by the National Aeronautics and Space Administration (NASA) in the US, and the nuclear power generation industry, as represented by the Nuclear Regulatory Commission (NRC), also in the US, were selected for this best-practice benchmarking exercise.

The aeronautics and nuclear power generation industries were chosen because, as discussed in detail below, formal and documented Risk Management approaches and methodologies have been extensively used in those industries for over three decades. NASA and the US Nuclear Regulatory Commission were chosen as appropriate organisations within those industries for formal study, because of the extensive and open use these two organisations have made of formal and rigorous Risk Management methodologies. Also, as described below, both organisations are governed, and indeed empowered, by a comprehensive documented framework that formally requires the application of formal Risk Management methodologies in their day-to-day work.

This chapter is divided into two parts. Section 7.2 describes the development and use of Risk Management approaches at NASA, and it reviews how the approaches used by NASA compare with the approach to Quality Risk Management developed here.

Section 7.3 describes the development and use of Risk Management approaches at the US Nuclear Regulatory Commission, and it discusses how the approaches used by the

US Nuclear Regulatory Commission compare with the Quality Risk Management approach developed here.

Where relevant, comparisons are made between the approach to Quality Risk Management developed in this research and that of either NASA or the US Nuclear Regulatory Commission. When important differences are identified between the various approaches, these are also commented upon in the text of this Chapter.

Although the approaches to Risk Management that have been developed by NASA and the US Nuclear Regulatory Commission do differ considerably in some respects than the approach to Quality Risk Management developed in this research, this comparative study found many examples of common '*best practice*' strategies in activities such as risk identification, control and mitigation, among others. These examples of best practice are discussed in detail below.

This review also resulted in the identification of several useful features inherent in the NASA and NRC approaches to Risk Management that could be beneficial to the Quality Risk Management methodology developed in this work. In this regard, a number of formal Recommendations are made in Chapter 8 of this thesis with respect to the incorporation of such features into the design of this Quality Risk Management methodology.

7.2 NASA's Approach to Risk Management

This Section reviews the evolution of Risk Management activities at NASA from the 1960s through to the late 1990s, and this is followed by a detailed review of the changes that took place at NASA during the 1990s which resulted in more highly formalised and expanded Risk Management activities at NASA.

7.2.1 Risk Management activities at NASA up until the late 1990s

Risk Management activities have been carried out at NASA for many years. During the *Apollo* projects and missions of the 1960s, for example, Risk Management activities were carried out in order to identify and mitigate risks to mission launch and success (139). Up until the mid to late 1990s, such activities were directly linked with how missions were classified at NASA, and risk was viewed as something to be minimised or avoided (139). Missions were classified into one of four classes: A, B, C or D; these classifications were based on mission priority and national prestige, among other things. This classification was rule-based, meaning that certain pre-defined rules determined various things up-front, such as how relative costs would be assigned to the mission, and the approach that would be taken to Risk Management. For example, Class D missions were missions which would generally cost 10% that of Class A missions, and the Risk Management approach for such missions was described in NASA's rule-based policy document, document no. NMI 8010.1a (132), as described below.

At that time, formal Risk Management activities at NASA usually occurred late in projects, after the design and hardware developmental work had ended. This approach placed a high reliance upon analysis and testing activities late in a project, post the design and hardware development work. The idea was that risks and defects would be identified and addressed before mission launch. NASA viewed this approach as delivering flight performance with minimum risk, and one in which all risk had to be minimized prior to launch (139).

In the early 1990s, NASA began to critically examine how it used Risk Management in its work activities, and it began to examine how improved Risk Management work might add value and decrease its accident and mission failure rates (139). NASA acknowledged that Risk Management was not a new concept for NASA employees, and that Risk Management activities had been in place at NASA for many years. But it also acknowledged that the use of Risk Management up to that time had been rather informal, and that the current approach to Risk Management had resulted in "a few failures" that had not been predicted or reduced in number (139).

One important finding that came out of this 1990s review (and which was later to be further developed at NASA) was that NASA had not in any way been making use of the concept that risk could be treated as a *commodity for trading* within a NASA project or mission (139). In this regard, there was no provision made at NASA for accepting a higher level of risk in one area within a mission, (for example, accepting a higher risk of power loss for a piece of hardware), if this could allow the risk associated with another area or part of the same project or mission to be substantially reduced. Thus, risks were not considered to be *resources* which could be strategically used, and risk was not *traded* from one area to another (such as between the areas of power, cost, scheduling, performance, mass, etc.). In practice, this meant, for example, that if significant progress had been made in reducing risk in one area of a mission, such as in the performance of a part of equipment, this was not used in any way as leverage when assessing what level of part redundancy might be required for the system that used that component or part of equipment.

7.2.2 NASA's move towards more formalised Risk Management activities in the late 1990s

In the late 1990's, there was a major drive at NASA to expand and extend its Risk Management activities, and to make such activities more formalised (139). NASA's office of Safety and Mission Assurance was charged with the task of developing core competencies in formal Risk Management methodologies, and to act as Risk Management consultants in NASA projects. This office would also support Risk Management planning activities and up-front risk assessments, and it would provide Risk Management training to NASA staff, as required.

During this drive towards the use of more formalised Risk Management approaches, NASA outlined the background to this work. It described how NASA's business was one which "injects uncertainty and creates inherent risk" and operates in an aerospace environment that was "harsh and unforgiving" (140). NASA recognised that its mission systems were highly complex and stated that "the essence of Risk Management [was] the essence of good project management" (140). In this regard, NASA stated that success depended "on identifying, understanding and controlling risk", and that the

acceptance of prudent mission risk was "the hallmark of NASA's approach", while at the same time fully attending to mission safety considerations (140). This shows the emphasis placed by NASA at that time on addressing risk in a more formal way than before, with a strong shift towards the use of a structured risk management process, utilising formal risk identification and risk analysis tools as an aid to decision making (140).

This move towards the use of more formalised Risk Management approaches at NASA during the 1990s was facilitated by two major initiatives in project and mission management. These were:

a) the development and adoption of a project and mission philosophy known within NASA as *FBC*, which stands for *Faster, Better, Cheaper*;

b) a modification of the FBC philosophy which resulted in an initiative at NASA called *Mission Success First.* (As discussed below, this latter initiative was triggered in 2000 following the Mars Climate Orbiter mishap of September 1999.)

The *Faster, Better, Cheaper* and *Mission Success First* initiatives were probably responsible for the most significant developments in the use of formalised Risk Management at NASA since the 1960s to date. Each is reviewed in turn below.

7.2.3 NASA's Faster, Better, Cheaper (FBC) Initiative

NASA described the FBC initiative as a "state of mind" methodology, representing a "dynamic transition from old to new", and a strategy that was designed to help NASA maintain world leadership in the aeronautics environment (141-142).

The consideration of risk was a central tenet of FBC; NASA stated that FBC was about delivering ever increasing performance in human/robotic space missions, quicker, with reduced risk, increased safety and lower cost (141). In FBC projects, continuous Risk Assessment and mitigation activities were regarded as essential, and in essence, FBC can be viewed as really a high level Risk Management methodology in itself.

As described in March 2000 by what became known as the Mars Climate Orbiter Mishap Investigation Board, the aim of the FBC philosophy was "to do more with less", by "enhancing innovation and productivity, while enabling new safe, cost-effective approaches to achieving mission success" (143). The desired state in FBC projects was to arrive at a design space in a project for which cost was well matched to the desired scope of the project, and where risk was not significantly affected by changes in cost, schedule or project scope (143). The Board stated that in the FBC scheme of things, project "cost should not be reduced – nor content increased – beyond the point where risk rises rapidly" (143).

With the advent of FBC at NASA, the use of formal Risk Management principles and methodologies became embedded into all NASA projects and missions, and right across the NASA organisation. This applied not just to high profile NASA projects and missions, but also to NASA's more day-to-day activities, such as procurement and acquisition activities. This was demonstrated by NASA's Risk Based Acquisition Management initiative (called *R-BAM*) of March 1999 (144), as outlined in the US Federal Register in July of that same year (145).

At a day-to-day, practical level, Risk Management was a key component of all FBC-based projects at NASA. Not only was the use of formalised Risk Management methods a definite requirement for such projects, Risk Management requirements were an integral part of the rules governing all FBC projects. These rules, which became known within NASA as the *FBC Rules of Engagement,* gave significant prominence to activities such as risk identification, risk reduction and risk communication. Further information on these FBC rules is provided below in Section 7.2.3.6 below.

7.2.3.1 The Development of FBC-based programmes at NASA

FBC had its origins in the early 1990s, when NASA began to look at how it did business, and how it could improve its rate of mission success (141). There was also a need to respond to the challenges presented by the information age, and by the global and competitive business environment which NASA faced in the 1990s (141). Other

factors, such as a declining NASA budget and a move from few to many missions, were also important drivers for the FBC initiative (141).

NASA recognised that its mission failures, of which there were several up until 2000, had not been the result of the introduction of new technology to flight, but rather, were the result of mis-management, mis-engineering, and a breakdown in communications among project teams and across NASA's institutional support base. NASA recognised that it had been trying to do "too much, too fast", and that there was a need to "slow down", and focus on project implementation and design (141, 142).

As part of giving more focus to project implementation and design considerations, NASA began working on how to manage projects with a challenging target, but with defined cost and schedule caps. The key requirements of these FBC projects and missions were a) the need for continual innovation, b) the maximising and efficient use of resources, c) the need to cross organisational boundaries, and d) the reduction of risk. For these projects and missions, no longer would only the technical aspects of the mission or project be the main focus of work. Now, cost and scheduling factors would be given greatly increased prominence, in an effort to reduce the rate of mission and project failure. This was the central tenet of the FBC approach (141).

FBC was not, however, about adding cost and schedule constraints to fixed mission scope projects; rather, mission cost, risk and required reserves were to be determined for a carefully defined mission scope in an upfront, planning process. Where costs and schedule had to be capped at the outset, FBC required mission scope to be sized to allow for such constraints (141).

Specifically with respect to cost issues, FBC was not so much about cutting costs as it was concerned with ensuring that budgets were appropriate for the project or mission at hand, and that missions and projects were adequately defined and scoped out with reference to their assigned budget. In this regard, NASA recognised that in some areas, such as with Mars Flight Operations, budgets had been "cut too deeply", and that this had to be rectified (141).

As FBC projects developed at NASA, so too did the nature of the FBC programme itself, and many of the key features of FBC were refined and documented towards the end of the 1990s. NASA's positive experiences with FBC throughout the 1990s led NASA to rolling FBC out organisation-wide, so that all NASA missions and projects would be subject to defined FBC rules by the early 2000s (141). FBC would in effect become a whole new way of doing business at NASA, and it represented a significant cultural change for NASA employees (141).

During the development and optimisation of the FBC initiative, NASA consulted widely between July 1999 and February 2000 to seek out the views and concerns of informed stakeholders (141). In this regard, both NASA staff and external partners and stakeholders, such as academic researchers and the aeronautics industry, were interviewed on how to achieve the goals envisaged under the FBC programme, and several useful recommendations were made by stakeholders (especially Industry), and many of these were acted upon. In March 2000, NASA published its Final Report on the FBC initiative (141). This outlined what FBC was, and how it would operate in the future. In this report, NASA described FBC as a methodology designed to help NASA find ways to acquire and keep "good people", do a much better job of infusing "advanced technology" into NASA systems, and do a much better job of incorporating "new methods", especially those promised by information technology advances (141). These components made up what were called the three 'cornerstones' of FBC: *People, Technology and Methods* (141).

7.2.3.2 How NASA's approach to Risk Management changed with the advent of the FBC initiative

With the development of the FBC environment at NASA, the old approach to Risk Management at NASA, as described in NASA's rule-based policy document titled 'Classification of NASA Payloads', document no. NMI 8010.1A, was effectively replaced in 1998 with NASA's Procedures and Guidelines document, known as NPG 7120.5 (139). This formally linked Risk Management with project management, stressing that Risk Management was an essential part of project management, and that effective project management depended on "a thorough understanding of the concept of

risk, the principles of Risk Management", and the establishment of a "disciplined Risk Management process" (139).

NASA's policy document NPG 7120.5 was direct in its requirement for Risk Management, stating: "The programme or project manager shall apply risk management principles as a decision-making tool which enables programmatic and technical success" (139). NPG 7120.5A, a revised version of this NASA policy document, required Risk Management work to begin much earlier in the lifecycle of projects that it had been in the past, at the mission design stages. The latter NASA policy document also required that a structured Risk Management plan be in place by the end of the formulation stage of a project, and before approval of the project, and that all risks would be "dispositioned before flight" (139).

To support the above requirements, NASA created the *Office of Safety and Mission Assurance*. This served as a Risk Management centre of excellence at NASA. As described by NASA's Dr. M. Greenfield in 1998, the Office of Safety and Mission Assurance had the "core competencies to serve as a Risk Management consultant to NASA projects" and provided NASA projects with "Risk/Resource Tradeoffs, Strategies, Consequences, Benefits, Mitigation Approaches" (132). Specific core competencies included such items as failure analysis resolution, and emergency preparedness planning (139).

NASA's focus on Risk Management as part of the FBC initiative was evident at the highest levels. For example, the goal of reducing NASA mission failure rates was listed among NASA's top goals and challenges for the 21st Century, which included such high level goals as determining if extra-terrestrial life exists, and establishing permanent human and robotic presence in space (146).

The above approach to Risk Management in the US aeronautics industry contrasts sharply with the present status of Quality Risk Management within the EU regulatory framework for GMP-regulated environments in a number of ways. For example, in the EU, there are, at the present time, no formalised official structures in place providing competencies in formal Quality Risk Management activities for GMP environments for either GMP Inspectors or Industry. In relation to Risk Management plans, not only is

there no similar EU GMP requirement in place for the generation of such plans, there is currently (December 2007) no documented requirement within the EU GMPs for Quality Risk Management to be undertaken as part of GMP. (This is set to change in 2008, however, with the planned incorporation of formal Quality Risk Management provisions into Chapter 1 of the EC Guide to GMP.)

With respect to NASA's dispositioning of risks before key activities take place, there is no similar requirement in place within the EU GMPs for key activities such as batch certification and release. At the time of writing, the development of Quality Risk Management activities within the EU pharmaceutical GMP environment is at an early stage, and from the author's experience as a GMP Inspector in the EU, much of this work is currently mainly retrospective in nature.

7.2.3.3 The FBC Concept of Treating Risk as a Resource

FBC allowed NASA to move from the aforementioned "rule-based" decision-making environment of the early and mid-1990s (as proceduralised via the NASA document NMI 8010.1a), to a more "knowledge-based" decision-making environment thereafter (139). Importantly, within the new FBC environment, risk was to be viewed at NASA as a resource which could be traded (139).

In this *knowledge-based* environment, as long as there was an appropriate level of mitigation in place for risks that were accepted in the sub-system of concern, risks in that subsystem of the mission could be treated as a resource which could be "traded" for risks in other sub-systems (147). Redundancy was a key feature of this risk-trading approach, and so was the concept of balancing risk mitigation activities "against available cost and schedule constraints" (147). In this respect, NASA developed a formal Risk Management tool called the Risk Balancing Profile Tool for this purpose (147).

It is important to note that NASA's Risk Balancing Profile Tool was a qualitative approach to assessing which risk mitigation strategies were appropriate for the mission

at hand, taking cost and scheduling constraints into account. This was not a quantitative approach.

The intent of NASA's risk trading and risk balancing approach was that, accepting a higher than normal risk in one sub-system may benefit the development of another subsystem, so that the overall mission risk could be optimised. NASA stated that "the time when every identifiable step was taken to avoid risk is being replaced by a faster, better, cheaper approach" and that "those days are now over" (147). At the core of this FBC philosophy was the need to determine "how much risk mitigation was enough, and for project managers to make informed decisions on where to spend his or her risk reduction dollars (147).

7.2.3.4 NASA's use of Risk-trading and Risk-balancing in FBC Projects

The idea behind NASA's Risk-trading and Risk-balancing approach was that, as long as there were appropriate and balanced risk mitigation strategies in place for high risks sub-systems, such risks could be accepted in that sub-system if doing so would benefit another sub-system in the project or mission, and if strategies to recover from the occurrence of those high risks were in place.

The aim in doing so was to reach a balance between the risk-mitigation activities that were to be implemented in order to achieve an appropriate level of mission success, and the cost and schedule constraints associated with the project or mission of concern (147). The ultimate goal of this approach was that the overall risk associated with the mission would be optimised and balanced against cost and scheduling constraints.

The sub-systems (or areas) within a NASA mission between which risks could be traded were the following: Spacecraft Power, Spacecraft Mass, Mission Performance, Mission Cost and Project Schedule (139). When a sub-system was identified in which risk mitigation activities were to be focused, several different risk mitigation strategies could be used. These included making use of hardware redundancy strategies, ensuring the use of only highly reliable components, ensuring that only highly reliable contractors were chosen to produce critical parts, or using other types of controls, such as the particle

impact noise detection tests that were often performed on hardware parts used in NASA missions (147).

At NASA, this risk trading and balancing process begins, or is triggered, when the "cost per unit of risk reduction" in any one sub-system increases significantly and becomes prohibitive in that sub-system (139). This is similar to what is sometimes called the *law of diminishing returns*, and is also reflected in Pareto analysis charts, which show that, often, a small portion of the risks in a system can account for a large portion of the overall cost associated with those risks – the so called 80/20 law.[12]

- ***Example of Best Practice in this Quality Risk Management Methodology:***

  The Quality Risk Management process used by the Quality Risk Management methodology developed in this work is similar in several ways to the above NASA risk trading and balancing approach.

  This Quality Risk Management methodology formally recognises, via Steps 6 and 7 of the Quality Risk Management process, that it is not necessary to reduce all risks below a certain risk threshold before they can be accepted, as long as there are controls (i.e. mitigation strategies) in place which mitigate against that risk, should the negative event which might lead to the risk in question occur. Indeed, this feature of the methodology is reflected in one of the twelve fundamental principles underlying the methodology discussed in Chapter 2 - that there may be some risks which cannot be eliminated or reduced to an acceptable level with current or realistic controls/resources, but which may be controlled to an acceptable level with improved detection or other measures, as determined on a case-by-case basis.

  The Guidance in place for Step 7 of the methodology further promotes this concept by ensuring that the team does not go 'overboard' in proposing controls to reduce a risk beyond that which is necessary. In addition, as in NASA's approach, this methodology makes clear provision for, and actually promotes, the putting in place

[12] For a useful discussion in this area, see "Production and Operations Management", by Muhlemann, A., Oakland, J. Lockyer, K. 6th edition, published by Pitman Publishing, 1992, pp263 – 264 and pp483 – 487.

of recovery or redundancy-type controls, via Steps 5 and 7 of the Quality Risk Management process.

While the concept of using the 'cost per unit of risk reduction' to trigger a risk trading and balancing process is a useful, data-driven approach, it does, by definition, require one to either know what is the cost per unit of risk reduction in any one sub-system, or be able to calculate it. Neither this Quality Risk Management methodology nor other Quality Risk Management methodologies used by the pharmaceutical manufacturing industry formally use cost per unit of risk reduction data when planning and deciding on risk mitigation activities. This is probably because the development of Quality Risk Management in the pharmaceutical manufacturing industry is still at its early stages, and mechanisms have generally not been formally developed to calculate and apply concepts such as the cost per unit of risk reduction. See Chapter 8, Section 8.5, for a recommended action for the pharmaceutical manufacturing industry in this regard.

As NASA, the use of redundancy-type controls is integral in the risk acceptance strategy (139). However, risk trading and balancing does not have to mean that higher risks can be assumed only on the basis of redundancy. Consider, for example, a highly redundant system design for a particular NASA mission. The design of the system may provide a high degree of mission performance assurance, for achieving long life missions. The system design, however, may be highly complex as a result of the use of redundant sub-systems for critical components, and the project may therefore be relatively expensive, due to this increased complexity and the need for extra components.

In this type of design, the risk of a component failure is mitigated via the design provision for a high degree of redundancy in the components and sub-systems used. This design is one that readily lends itself to risk trading, as some of the redundancy built into the design may be traded for the use of more reliable components. The idea here is that the level of component redundancy can be reduced if highly reliable components are used, as these usually provide more assurance that component failure events will not occur. Thus, component redundancy may be *traded* for component reliability. This approach is one which can easily be facilitated at NASA because

NASA formally differentiates between components on the basis of their reliability. NASA classifies components into three types (147):

- Class S components: These are components that are customised to the application at hand. In relative terms, they are the most expensive components used at NASA, but are also the most reliable and have the highest specifications.

- Class B components: These are components that are of more moderate cost, being less customised in design or build than Class S components. They are also considered somewhat less reliable than Class S components.

- COTS components: These *Commercial-off-the-Shelf* components are normally readily available and cheap, in comparison to either Class S or B components, but have less reliability.

7.2.3.5 The role of People and Teams in FBC Projects

In March 2000, NASA stated that first and foremost, FBC was about people, and that "leaders and people make FBC work, not words on paper or memory" (141). A major emphasis of FBC was thus on teamwork and on team leadership.

FBC promoted the need to empower individuals, so that they might innovate, become more efficient, and "take risks on exciting endeavours" (141). FBC was also about people being willing to be held accountable – in success or in failure (141).

At the core of the FBC philosophy was the principle that teams and team leaders should be permitted to decide how much risk mitigation was enough, and that project managers were empowered to make informed decisions on where to spend ... risk reduction dollars (147). Developing teams and their leaders was highly formalised within NASA's FBC environment, and certification programmes were developed for Team Leaders and project teams in general (141). At NASA, such certification programmes were regarded as essential in the FBC environment, as FBC Teams had the authority to

make risk-acceptance decisions, while assuming an increased level of accountability for the project at hand. Interestingly, while NASA required teams to have a careful mix of "scarred experience and bright energetic youth" (146), a formal quantitative assessment of the Team Leader's and the team's experience and expertise base was required.

In contrast, within the pharmaceutical manufacturing environment, there is currently little time spent on preparing or certifying people to lead or to participate on Quality Risk Management teams. From the author's experience as a GMP Inspector, there is often little thought given to whether some people may or may not be suited to Quality Risk Management work. The concept of having certified individuals for Quality Risk Management work, similar to NASA's "professional driver" qualification for leading Risk Management project teams, is not yet widely in place in the pharmaceutical manufacturing environment, and there is more to do in assessing the suitability of individuals for their potential as Quality Risk Management team leaders, or Quality Risk Management team participants.

The above FBC philosophy at NASA empowers and actually promotes FBC teams to take increased risks when working on less costly projects, so that an environment for achieving major breakthroughs may be facilitated. In this regard, entrepreneurial behaviour and 'out of the box' thinking were encouraged and rewarded at Team Leader level, and there was less mission oversight generally in place (142). There was also an acceptance that such missions were high risk, and the required mission success rate for such projects was lower than with more expensive NASA projects, being set at greater than 8 out of 10 (141).

With more expensive projects at NASA, FBC required a higher level of mission oversight, and it allowed less entrepreneurial behaviour at Team level. Consequently, for such missions and projects, FBC teams had less ability to take risks, and efforts were made to reduce the overall risk of the mission to low. For the most expensive NASA missions, the required mission success rate for such projects is set at greater than 999 out of 1000 (141).

The above approach contrasts sharply with the use of Quality Risk Management in the pharmaceutical manufacturing environment generally, where cost considerations do not

usually lend themselves to justifying the assumption of higher risks, either in pharmaceutical production processes and controls, or in pharmaceutical products. There is a basis for this differing approach, as notwithstanding legal and regulatory constraints, in the pharmaceutical manufacturing environment, the consequences associated with failure can be quite different than those associated with aeronautics projects of the type run by NASA. In the former environment, there is usually more at stake than simply product or process failure for the cost expended, and the loss of national prestige is not normally a relevant consideration. Unlike the aeronautics area, in the GMP environment, a great many people or other animals may be affected adversely by a defective medicinal product or manufacturing process, no matter what the cost of producing that product or running that process was.

NASA has reported that the transition to FBC projects and missions was highly challenging in the area of people, as FBC required many more project teams, with defined training needs (141-142). NASA stated that this was a major learning, and one for which the Agency was not prepared for (141). This was a lesson that the GMP environment can learn from NASA's experience. See Section 8.5 in Chapter 8 of this thesis for a recommended action for the pharmaceutical manufacturing industry in this regard.

*

Finally in the area of people within the FBC environment, during NASA's consultation with industry on its FBC initiative during 1999 and 2000, one of the risk-related comments made by Industry about the FBC programme was that NASA needed to ensure that FBC project work did not lead to staff burnout in project teams. Industry felt that there was a danger with FBC that continuous workloads could be well in excess of what was reasonable, and that FBC work could become an "error-prone environment", where heroic efforts might occur but may not be able to be repeated.

The aeronautics industry expressed the concern that such continuous workloads could also lead to the loss of competent people to other industries, resulting in increased risk due to loss of continuity on a project. (The so-called *brain-drain* effect was actually one of the very things that the FBC programme was designed to reduce in the first

place!!). In light of this, the aeronautics industry proposed the establishment of jointly sponsored "programme management training" events for both NASA and Industry staff.

7.2.3.6 The rules behind FBC Projects at NASA

The FBC programme at NASA carried with it a formal set of rules which were mandatory for both project teams and NASA institutions to follow. These rules were known as the FBC '*Rules of Engagement*', and both NASA institutions as well as NASA project teams were subjected to their own specific Rules of Engagement.

There were several rules in the FBC Rules of Engagement which specifically related to Risk and Risk Management activities during FBC projects. Three of the main rules were as follows (141):

1. FBC project teams were required to conduct continuous and rigorous Risk Assessment and mitigation activities throughout development and operations;

2. FBC project teams were required to size mission scope within resources to provide for acceptable risk and adequate reserves;

3. FBC project teams were required to establish and maintain "metrics for mission risk and Technical/Cost/Schedule performance" and to maintain what was called a '*Mission Risk Signature*' for each project (141). NASA facilitated this by having a metric status sheet in place for each FBC project, which showed the compliance status of various aspects of the project using green, yellow and red labels. This approach also involved clearly estimating and documenting the overall risk that was associated with each project. This risk, which was called the *Mission Risk Signature* for the project, was expressed both in terms of cost & schedule risk, and as mission risk. These two types of risk were then tracked in FBC projects over time, from initial project concept to launch and land events (where applicable). This approach recognised that some initial risks may have been determined to be high, and while this was permitted, FBC required that good risk assessment and mitigation were in

place for such risks, and that the initial high risk was reduced to an acceptable level prior to launch and throughout operations thereafter.

- ***Example of Best Practice in this Quality Risk Management Methodology:***

  The Quality Risk Management methodology developed in this work has several features that render it similar to NASA's FBC Risk Management approach, as underlined by the above three FBC rules.

  For example, this methodology offers a rigorous Quality Risk Assessment and Risk Mitigation process, and provision is made for mandatory periodic review activities. This is similar to the FBC requirement for continuous / rigorous Risk Assessment and Mitigation throughout development and operations.

  As in NASA's approach, resource considerations are a central feature of this methodology, with Step 8 of the Quality Risk Management process focused on formally evaluating and determining the required resources for each control associated with each risk.

  Reserve considerations are also a feature of the methodology developed here, as a major focus of Steps 5 & 7 of the Quality Risk Management process is on controls which provide back-up and redundancy measures. This is similar to the reserves component of NASA's FBC Rules of Engagement when accepting risks.

While this methodology uses green, yellow & red labels when classifying risks at Steps 5-7 of the Quality Risk Management process, this methodology makes less use of such colour-coded risk labels than NASA's FBC approach. For example, in this methodology, colour-coded risks are not formally incorporated in any way into the Validation Master Plan for the site or project, and the overall Qualification and Validation status of the item under study is not documented using colour coding techniques in the Validation Master Plan at the end of the Quality Risk Management exercise.

It would be useful to adopt NASA's approach for tracking the status of particular items from a risk-based validation and qualification perspective using a colour coding scheme similar to that used by NASA, as it is intuitively simple to use and follow. Doing so would enable the Validation Master Plan to visually show, at any one time, whether a manufacturing process, facility, item of equipment etc, has been subjected to any formal Quality Risk Management work, and what the general outcomes of that work were. See Section 8.6 in Chapter 8 of this thesis for a recommended action in relation to modifying Step 10 of the Quality Risk Management process to incorporate the above NASA idea.

As stated above, not only were there FBC '*Rules of Engagement*' in place for FBC project teams and their leaders, there were also specific Rules of Engagement in place for *NASA institutions*, and several of these specifically related to Risk and Risk Management activities.

For example, under FBC, NASA institutions were required to educate the public more clearly on the challenges and risks associated with the project as well as the exciting potential return on their space exploration investment. This shows that risk communication has been an area of concern for NASA, and indeed, one of the top ten official challenges for NASA at that time (March 2000) was to outreach to the public more effectively, to engage them, involve them, and get them to understand both the risk and the major payoff potential for NASA (141, 142).

- ***Example of Best Practice in this Quality Risk Management Methodology:***

  The Quality Risk Management methodology developed in this work likewise places importance on risk communication activities, and this includes risk communications to the public. This is an area, however, that has been largely underdeveloped in the pharmaceutical industry, and more work is required in order to assist the public in understanding the risks associated with medicinal products.

Another risk-related rule for institutions carrying our FBC projects relates to the aforementioned area of *Risk Signatures*. This is similar to the *Risk Signatures* requirement for project teams, described above, and the institution in question must establish and maintain a Risk Signatures programme.

Finally, in relation to the FBC rules of engagement, NASA has stated that not everyone can pick up the FBC rules of engagement and succeed at FBC (142). Perhaps the pharmaceutical manufacturing environment can learn from NASA's experience in this area, and recognise the importance of qualifying individuals for Quality Risk Management work.

7.2.3.7 Learning from past mishaps and failures in FBC Projects

A major part of NASA's FBC was the focus given to learning from past mishaps and failures. In this regard, formal structures and programmes were put in place at NASA to capture and evaluate past failures and near misses. These include the NASA *Integrated Action Team* and the *Lessons Learned Information System* (LLIS) (139).

In the pharmaceutical manufacturing environment, there are also normally systems and controls in place which are designed to identify lessons learned from mishaps, such as process deviation and Out of Specification investigation procedures, but these are perhaps not as clearly focussed on extracting lessons to be learned from mishaps and near misses as the NASA programmes are.

The above focus on learning from past mishaps and failures permeates right across NASA, as is evident from the design of the overall FBC programme, where, it is worth noting, the *Methods* cornerstone of FBC carries a formal requirement to maintain *Lessons Learned* databases. Real examples of such work included the Mars Climate Orbiter Mishap Investigations of 1999 and 2000 (discussed in Section 7.2.4 below), and investigations into various failures which occurred with the Space Shuttle during the 1990s. NASA has even worked to highlight and discuss lessons learned at special symposia sponsored by NASA on lessons learned!!

- ***Example of Best Practice in this Quality Risk Management Methodology:***

  The Quality Risk Management methodology developed in this work likewise places an emphasis on the value of 'near miss' data, and it encourages the capturing and reporting of near miss data in the Quality Management system in place at the facility employing this Quality Risk Management methodology.

In the pharmaceutical manufacturing environment, there are usually rigorous, risk-based and formal procedures in place to investigate deviations and non-conformances; this includes deviations from approved procedures, non-conformances with respect to company policies and procedures, deviations from in-process control requirements, and out of specification batches. In the author's experience as a GMP inspector in the EU, there is usually much less of an emphasis placed on capturing information on near miss events, where no deviation or non-conformance may have actually occurred. Such information is valuable, however, in the context of Quality Risk Management activities, because it can help identify what can go wrong with the item under study, and the frequency of it occurring. See Section 8.5 in Chapter 8 of this thesis for a recommended action in relation to capturing information on near miss incidents.

7.2.4 The further development of Risk Management at NASA following the Mars Climate Orbiter mission failure

The second major development in NASA's Risk Management programme was triggered in September 1999, when NASA experienced a serious mission failure in its Mars Surveyor programme. This failure was to have significant repercussions for project management activities at NASA in the years thereafter, and this impacted upon the use of Risk Management methodologies at NASA in the years to come. In addition, to the author's knowledge, this was the first time that risk-based validation activities at NASA were highlighted as an area of explicit concern following a mission failure.

As part of NASA's Mars Surveyor programme, a spacecraft known as the Mars Climate Orbiter was launched in December 1998, carrying instruments to map and study both

the surface of Mars and its atmosphere. This was a programme that had been developed and executed under NASA's FBC project philosophy. On September 23, 1999, the spacecraft was lost when it entered the Martian atmosphere at a lower then expected trajectory. Efforts were made to restore communication with the spacecraft, but these were unsuccessful, and the mission failed (148).

Two detailed investigations were carried out into this mission failure. The first was completed in late 1999, and it quickly established the root cause of the mission failure. This related to the failure of computer programmers at NASA to use metric units in the coding of a ground software file known as 'small forces', a piece of software that was used in trajectory models for the spacecraft (148). The second investigation occurred from late 1999 through to the early part of 2000, and this focussed on the learnings and lessons that could be gained from the accident (143).

The second Investigation Board, in its final report dated March 13th, 2000 (143), presented several important learnings from the errors and contributing factors that led to the Mars Climate Orbiter failure, (as well as several other earlier NASA missions which had also failed).

At a high level, the Investigation Board found fault with how FBC projects and missions had been managed at NASA up to that time, and in more specific terms, it highlighted flaws in NASA's approach to Risk Management and validation activities generally (143). These were considered to be among the most important and frequent contributing factors to the failure of the Mars Climate Orbiter and six other failed missions that were reviewed by the Board as part of its Mars Climate Orbiter Mishap Investigation (143).

On NASA's use of the FBC philosophy, the second Investigation Board strongly supported the FBC approach, but it found that "too much emphasis" had been placed "on cost and schedule reduction", and that FBC projects and programmes had "failed to instil sufficient rigor in risk management throughout the mission lifecycle" (143). For example, the Board found that there had been "a lack of systematic analyses of 'what could go wrong'" with the Mars missions, and that "no fault tree or other *a priori* analyses of what could go wrong" had been performed (143).

The report of the second Mars Climate Orbiter Investigation Board stated that the above factors had increased risk to an unacceptable level on these projects. Specifically in this regard, the Board found that the Mars Surveyor Programme had agreed to "significant cuts in monetary and personnel resources to support the Mars Climate Orbiter mission, as compared to previous projects", and that the Mars Climate Orbiter project "failed to introduce sufficient discipline in the processes used to develop, validate and operate the spacecraft" (143).

7.2.4.1 NASA's Mission Success First initiative

When recommending changes and corrective measures in response to the failure of the Mars Climate Orbiter and other missions, the Investigation Board proposed a sweeping range of changes and other measures, many of which related to Risk Management and validation practices and activities. These were collectively contained within a new vision for NASA programs and projects, one that would support the FBC philosophy but which would improve mission success (143). The name given to this new vision at NASA was '*Mission Success First*', and it would require the creation of "a new NASA culture and new methods of managing projects" (143).

Among the many changes envisaged under the *Mission Success First* initiative, those relating to Risk Management and validation were among the most prominent. For example, with respect to Risk Management, the report mandated that "greater attention" be paid to "risk identification and management", and that risk should be "treated equally as important as cost and schedule" (143). The use of risk balancing and trading approaches was strongly supported, but this would now not be accomplished independently of any predefined dollar cap.

The Investigation Board also developed a detailed checklist for projects executed under the *Mission Success First* philosophy that would serve as "a 360 degree benchmark tool to identify and reduce potential risk" (143). Risk Management considerations were a key component of this checklist, and these were not just aimed at a conceptual level, they required specific Risk Management-related work activities to be completed. For

example, the checklist required the project team to confirm that "single-point failures had been identified and justified"; that potential failure scenarios had been "identified and modelled", and that, in the project of concern, there was a culture that "never stops looking for possible failure modes" (143).

With respect to validation activities, the Board explained that more rigorous validation practices might have helped avert the software error that had occurred with the Mars Climate Orbiter instrumentation, as evidence had been found that "verification and validation at the module level and of the navigation algorithms at the subsequent sub-system level did not detect the [software coding] error", despite evidence of the anomaly early on (143).

As a result, the Board recommended a markedly increased validation effort on NASA projects going forward, from the simplest component or module to the most complex system. The Board stated that "end-to-end verification and validation" conducted via simulation or other testing of hardware/software must be structured to permit traceability and compliance with mission and derived requirements, and that "final end-to-end verification and validation of all mission-critical operational procedures must be performed" (143). As part of this approach, the Board also mandated that mechanisms to minimise technology-related risk should be employed to validate high risk technologies prior to their use on science missions.

Specific verification and validation requirements were also formally written into the project checklist that was developed under the new Mission Success First philosophy.

- ***Example of Best Practice in this Quality Risk Management Methodology:***

  The Quality Risk Management methodology developed in this work has several features that are similar to what was recommended by the second Mars Climate Orbiter Investigation Board.

  For example, this methodology was designed to identify, assess and manage risk at an appropriate indenture (or sub-system) level in the system or item under study, in order to facilitate meaningful and appropriate risk-based validation activities.

Such validation considerations extend not just to the controls that are identified via Risk Control measures (at Step 7 of the Quality Risk Management process), they also apply to the controls that are documented earlier in the Quality Risk Management process, at Steps 5 and 6 of the process, which relate to risks for which no additional risk control measures may have been required.

The second Mars Climate Orbiter Investigation Board also found serious lapses in the mission assurance function of the Mars Climate Orbiter project, such as the absence of a problem reporting process (known at NASA as an *Incident, Surprise, Anomaly* reporting system), which were shown to be directly related to the software problem which led to mission failure (143).

It was concluded that the Mars Surveyor Programme had not adequately instilled "a mission success culture" that would shore up the risk introduced by resource reductions, and that deficiencies in work processes and in project leadership had introduced sufficient risk to compromise mission success to the point of mission failure (143).

7.2.5 Continuous improvement in NASA's approach to Risk Management

By 2000, following the Mars Climate Orbiter mission failure, work was underway at NASA to identify and analyse deficiencies in its Risk Management activities. Approximately 175 recommendations for improvement were made following this review. The deficiencies in question related to a number of different areas, including NASA's risk identification and analysis activities. Poor practices in risk mitigation and risk tracking were also noted for criticism, as was the limited use made by NASA of Risk Assessment tools.

In the pharmaceutical manufacturing industry, the application of Risk Management tools has likewise been narrow. From the author's review of the literature, from his experience as a GMP inspector, and from discussions with companies and other inspectors (via for example at PIC/S-sponsored meetings during 2006 and 2007), most

applications of Quality Risk Management in the pharmaceutical manufacturing industry to date appear to be related to computerised systems, equipment and systems qualification, and manufacturing processes. In addition, it is usually the case that only a small number of the above areas will have been subjected to formal Quality Risk Management exercises within any one company.

During the development of this methodology, this problem was recognised, and one of the specific design criteria for the methodology was that the methodology should have wide applicability across the GMP environment.

While the above self-inspection work at NASA had identified problems and limitations in NASA's use of Risk Management methodologies, it nevertheless demonstrated the advanced level to which Risk Management had become embedded into the work of the US aeronautics industry by the year 2000. This contrasts sharply with the state of Quality Risk Management in the pharmaceutical GMP industry at the present time, where the use of formal Quality Risk Management methodologies is just beginning in many companies.

7.2.6 The Risk Management process used by NASA

As discussed above, Risk Management activities were a formal and integrated component of NASA's FBC project philosophy. In this regard, NASA's Office of Safety and Mission Assurance was the department charged with driving and overseeing the implementation of Risk Management at NASA, with one of its roles being simply but importantly "understanding risk" (139).

Before reviewing NASA's use of specific Risk Management tools, it is helpful to review the general Risk Management process which was, and is, used at NASA (149).

At a high level, the Risk Management process used at NASA has five main components (149). These are:

1. **Identify:** Risk issues and concerns are formally identified;
2. **Analyse:** The impact, severity, probability of occurrence and time-frame associated with risk issues are evaluated, and risks are classified and prioritised;
3. **Plan:** Here, it is decided what, if anything, should be done about specific risks;
4. **Track:** Risk metrics are monitored, and risk mitigation actions are verified or validated;
5. **Control:** Risk mitigating actions are executed, risks are closed-out, contingency plans are invoked, and risks are tracked.

There are several important similarities between NASA's Risk Management process and the Quality Risk Management process utilised by the Quality Risk Management methodology developed in this work. These are discussed below, as examples of Best Practice in this Quality Risk Management Methodology.

- ***Examples of Best Practice in this Quality Risk Management Methodology:***

  Both approaches are similar with respect to the formal focus each process gives to validation activities.

  Both approaches recognise the principle that "one size does not fit all" with respect to what risks may be acceptable and which may not be. NASA has stated that, while "the mission risk acceptance process is the same regardless of mission, the degree of acceptable risk will vary greatly, depending on mission-unique considerations (149)". In the methodology developed here, Step 3 of its Quality Risk Management process requires a formal and documented assessment (followed by acceptance or customisation) of the default definitions given for probability of occurrence, severity and detection. This occurs each and every time the Quality Risk Management methodology is used. This is important because the above definitions agreed at Step 3 of the Quality Risk Management process directly determine what risks may be accepted and what risks may not. This is achieved by means of the Risk Table presented on the Laminated Card provided with the methodology. As in NASA's process, in this methodology, the risk acceptance process is the same for all applications of the methodology, but by virtue of the design of Step 3, the degree to which risks are deemed acceptable may vary greatly from one situation to another,

Both processes place a strong emphasis on the importance of involving stakeholders when communicating the results of Risk Management activities, particularly in terms of the risks that may be considered acceptable, without further risk reduction. The NASA Risk Management process requires both management and stakeholders to be a part of the mission risk acceptance process (149). In the methodology developed here, the team performing the exercise are required, during Step 10 of the process, to consider and document which stakeholders should be communicated with in terms of the risks identified during the Quality Risk Management process, the risk acceptance decisions that were made, among other things.

Both processes place a high degree of emphasis and rigor in the risk assessment process associated with hazards or potential negative events. This is not the case with some Risk Management tools, such as HACCP (48, 49) and Fault Tree Analysis (45).

There are also some key differences between NASA's Risk Management process and the process used by the methodology developed here. For example, the methodology developed here goes further in the area of validation than does the NASA approach - the latter primarily applies verification and validation activities only to risk mitigating controls, while the methodology developed here applies qualification and validation activities to controls involved in both pre- and post-risk mitigation activities. Also, while both processes contain formal risk communication activities, at NASA, risk communication is an activity that occurs at any time during the Risk Management exercise, while in this methodology, risk communication occurs mainly near the end of the Quality Risk Management process, at Step 10.

7.2.7 The specific Risk Management tools used by NASA

Prior to 2000, NASA had traditionally used FMEA (46-47) as its main Risk Management tool, which NASA has generally described as a *Risk Assessment/Risk Management* methodology.

Other tools were used as well, such as Fault Tree Analysis (45), for example, when a formal and vigorous root cause analysis was required. NASA's own *Risk Balancing Profile Tool*, described in detail earlier, was also used when risk trading and balancing activities were required, in order to identify a balance between risk mitigation strategies and "available cost and schedule constraints" (147).

NASA has also made use of several other risk mitigation strategies, and while these may not be considered to be formal Risk Management tools, they have been important elements in NASA's attempts to manage and address mission risks. One such example is NASA's *Lessons Learned Information System* (LLIS). This is a formal system that is designed to formally capturing and documenting lessons learned from NASA projects and missions (140). NASA also has carried out considerable work on understanding how accidents occur, and what causes NASA accidents and mission failures. The branch of study known as *Normal Accident Theory* has been given considerable attention by NASA's Office of Safety and Mission Assurance in its efforts to prevent accidents from occurring (90, 150). This is discussed in more detail below.

7.2.7.1 The use of Probabilistic Risk Assessment at NASA

In the late 1990s, NASA began "broadening its repertoire" of the Risk Management tools it used, and had begun to systematically use a more comprehensive set of tools collectively called Probabilistic Risk Assessment (151). Probabilistic Risk Assessment (PRA) is currently the main Risk Management methodology used by NASA, and is generally used for low-probability, high-consequence events for which insufficient statistical data exist as to their likelihood of occurrence (151).

NASA has described PRA as a "systematic, logical and comprehensive discipline that uses tools like FMEA, FTA, Event Tree Analysis (ETA), Event Sequence Diagrams (ESD), Master Logic Diagrams (MLD), Reliability Block Diagrams (RBD), etc, to quantity risk (151)."

NASA actually had begun using PRA before and during the Apollo space programme of the 1960s, but its use remained relatively low until after the year 2000. Like other Risk

Management tools, PRA is concerned with addressing the basic question: what can go wrong with the item of concern in the Risk management exercise? (152) The severity of a failure and the likelihood of the resulting undesirable consequences are also determined and evaluated via PRA, in a quantitative, numerical fashion (152). At NASA, PRA is principally concerned with assessing what can go wrong with *technology*, as indicated by NASA's reference to the "studied technological entity" when discussing its use of PRA techniques (152) at NASA.

NASA has stated that PRA is used at NASA to support strategic decision-making, to identify accident pathway end states, to support risk acceptance decisions, and, when risk is considered to be too high, to help assess the various possible options available for risk reduction activities, such as Space Shuttle upgrades (151-152). PRA is also used for design work and with systems under development, to "guide trade-offs" between safety, reliability, cost, performance, and other "tradable resources" (151). NASA's use of Risk Balancing approaches, described earlier, to trade risk in one area for another is an example of this (147).

NASA has demonstrated how PRA approaches have supported design-related decisions, by citing examples such as the application of *Event Tree Analysis* (50, 69) to the design process of a tyre used on the space shuttle (140). The tyre rolling over a hazard is chosen as an initiating event for an accident sequence, and as the event tree progresses, it is demonstrated how a redesign of the tyre can dramatically and quantitatively reduce the failure rate of the tyre when it rolls over a hazard.

Another example which demonstrates how PRA has been used at NASA is the *dead battery* scenario. Firstly, a Fault Tree Analysis exercise (FTA) was performed in order to identify the causative events (and their associated probabilities) leading to the dead battery. Next, an Event Tree Analysis (ETA) exercise was performed to help quantify the probability of success of the various related mitigating strategies for the dead battery (140). In this way, NASA demonstrated how PRA has been applied in practice, and its relative importance in risk mitigation work.

From a review of the available literature on NASA's use of PRA, it is evident that, to date, the use of PRA at NASA has centred around the application of a variety of

individual Risk Management tools, mainly FMEA, Master Logic Diagrams, Event Tree Analysis, Fault Tree Analysis, and Human Reliability Analysis techniques. In this regard:

- FMEA and Master Logic Diagrams are used by NASA to help identify the initiating events that can lead to accidents or mission failure (152).

- Master Logic Diagrams, which are very similar to high level Fault Tree Analysis diagrams, are used by NASA to identify the most important failure initiators in the item under study, and the less important failure initiators are screened out.

- Event Tree Analysis exercises are then performed at NASA to construct accident sequences from initiating events to their potential end states, and to assess the controls in place which may prevent the accident sequence from occurring. (NASA use methods such as thermal, fluid, structural and other engineering analysis techniques in order to develop such accident sequences.)

- Fault Tree Analysis is then employed to help quantify the probability of initiating events occurring, and the probability of success or failure of the various accident mitigating control strategies.

Note that in cases where the probability of an event is well known from past experience, NASA has stated that statistical actuarial data can be used if the uncertainty in these data are acceptably low (152). For rare events, e.g. system failures, for which there is no past experience at all or where the available data are sparse, probabilistic failure methods are developed with deductive logic tools such as Fault Tree Analysis, or inductive logic tools such as FMEA (152).

- ***Example of Best Practice in this Quality Risk Management Methodology:***

  The Quality Risk Management methodology developed in this work likewise uses a screening process similar to the above NASA approach. Here, the most important potential Negative Events are selected from a set of proposed potential Negative

Events during Step 4 of the process for formal and rigorous assessment via the remaining steps of the Quality Risk Management process. In addition, a key feature of Steps 5, 6 & 7 is the critical assessment of risk mitigating controls, and this is similar in principle to NASA's use of Event Tree Analysis.

There are also differences in both approaches. For example, while the methodology developed in this work offers a qualitative approach to the application of formal Quality Risk Management to the item under study, the NASA PRA approach is quantitative in nature. In this regard, the application of PRA methodologies at NASA results in a *numerical analysis* of accident scenarios, with the generation of what are known as graphical risk curves, enabling uncertainty values to be expressed quantitatively. Within PRA, and as indicated above, the use of Fault Tree Analysis at NASA is also quantitative, requiring a satisfactory knowledge of the failure rates of components, at what is called in FTA terminology, the *basic event level* (45). This quantitative approach relies upon known or estimated rates of failure of components (in both hardware and software) being available, as well as rates of the occurrence of human error.

Notwithstanding the above, NASA also makes formal use of qualitative Risk Management methods, which are employed to characterise hazards, failure modes and their effects in a more qualitative way. Given the early stage of development of formal Quality Risk Management methodologies within the pharmaceutical manufacturing industry at this time, it is perhaps not unexpected that more qualitative methodologies have been the predominant type of approach used in that industry to date.

7.2.8 The importance of System Complexity and Coupling considerations in NASA's approach to Risk Management

When describing the evolution of Risk Management activities at NASA, NASA's *Office of Safety and Mission Assurance* has stated that, in the past, the theory that "accidents can be prevented through good organisational design and management" was prevalent (90). However, NASA has recognised that this approach did not work with what it calls

complex and tightly coupled systems, and that, as suggested by Normal Accident Theory (150), accidents with such systems are inevitable.

NASA describes *complex* systems as systems with:

- Design features such as branching and feedback loops;
- Unfamiliar, unplanned or unexpected sequences which are not visible or not immediately comprehensible;
- Opportunities for failures to jump across subsystem boundaries.

NASA describes *tightly coupled* systems as having:

- Time dependent processes that cannot wait;
- Rigidly ordered processes (as in Sequence A must follow B);
- Only one path has a successful outcome.
- Very little slack in the system, as the system requires precise quantities of specific resources for successful operations (90).

With complex and tightly coupled systems, NASA has stated that there was a need to better understand how such systems can give rise to accidents, and how the risks of such accidents may be reduced (90). When training staff on the implications of Normal Accident Theory for NASA systems, NASA has cited examples of simple everyday events, such as missing an important meeting at work as a result of a set of unforeseen events at home that morning, to demonstrate how "a failure in one part of a system may coincide with the failure of an entirely different part, and how this unforeseeable combination can cause cascading failures of other parts (90)."

NASA has demonstrated how, in complex and tightly coupled systems, failures can be the result of many seemingly unconnected causative events, and result from interactions that were not in the design intent of the overall system. The "unravelling" (or accident pathways) that result are often complex and "have an intelligence of their own, exploiting circumstances that no engineer could reasonably plan (90)." Importantly, NASA has stated that with complex systems, combinations of such events are

"practically limitless", and that these "cascading failures can accelerate out of control, confounding human operators" and denying any chance of recovery (90).

As part of its FBC initiative and the Risk Management activities that formed a key part of FBC, NASA recognised that many of its own systems can be characterised as being complex and tightly coupled, and NASA began formal work in the late 1990s to overcome the risks of accidents with such systems. NASA's efforts in this area can be summarised under two general headings: *Increasing System Reliability*, and *Understanding and Reducing System Complexity & Coupling*. Each of these is discussed in turn below.

7.2.8.1 Increasing System Reliability at NASA

As a means of increasing the reliability of complex and tightly coupled systems, an important feature of NASA's efforts in this area has been the use of redundancy in equipment and in mission designs. This is so that if a failure occurs, there is a back-up system or control in place which can counter the effects of that failure. NASA's approach also recognises the value in having continuous operations, with operator training and work simulations, in order to increase system reliability. In this regard, uniform actions by operators are encouraged in order to instil a culture of reliability.

One drawback of using redundancy as a risk control measure is that redundancy adds complexity, and thus presents opportunity for new accidents. Thus, NASA cautions on the overuse of redundancy in system design, stating that redundancy is no longer the automatic answer (90).

- ***Example of Best Practice in this Quality Risk Management Methodology:***

  The Quality Risk Management methodology developed in this work likewise promotes the use of redundancy as a risk mitigation activity, as it provides a means of reducing the severity of the consequences of a potential negative event.

This occurs in Steps 5 and 7 of the Quality Risk Management process. Examples on the meaning of redundancy in this context are given in the Guidance presentation provided in the Training & User's Manual which accompanies this methodology (as described in Chapter 6).

Like NASA's approach, this methodology recognises the danger in overusing redundancy in order to reduce severity ratings for potential negative events. Thus, there are other options available in the methodology to reduce or control risks. For example: a) the methodology makes provision for identifying preventative, non-redundancy controls, which may be effective in reducing the probability of occurrence of a potential negative event, and b) the methodology allows risks to be left high, as long as alternative measures (perhaps based on detection controls), are put in place via either steps 6 or 7 of the Quality Risk Management process, to control the risk to an acceptable level.

7.2.8.2 Understanding and Reducing System Complexity & Coupling at NASA

With respect to system complexity, NASA has found that it is important to understand and identify those systems that are complex and which can be described as being *coupled*, so that risks presented by complexity and couplings can be managed. To this end, NASA has found that formally capturing and analysing data on close calls, incidents and mishaps is useful when trying to identify complexity and coupling in systems, as this is effective in identifying unforeseen complex interactions in tightly coupled systems (90).

In this regard, NASA promotes moving beyond the normal accident investigation pathways, which often only focus on operator error, inadequate training, faulty system design, mechanical failure, etc, towards investigations which give adequate attention to near-miss events, close calls, incidents and mishaps. NASA promotes closer scrutiny of these events, because "root causes of potential major accidents can be uncovered" through careful analysis in this area, and meaningful and proper corrective actions for the prevention of future accidents can then be developed (90).

- ***Example of Best Practice in this Quality Risk Management Methodology:***

  The Quality Risk Management methodology developed in this work is similar to the above NASA approach, in that, when potential negative events are being identified at Step 4 of the Quality Risk Management process, and when the causes of such are determined at Step 5, any available near-miss data are required to be taken into account, and evaluated thereafter.

It is well established that when identifying potential failure modes, it is useful to review obvious sources of information, such as data on process deviations, batch rejects, product complaints and defects, production problems, qualification & validation incidents, reasons for change controls, etc. However, one area that is often overlooked in formal Quality Risk Management methodologies is the occurrence of near miss events, or problem incidents that almost occurred. Near miss incidents can provide valuable and real information on potential failure modes and their frequencies, but they are often not formally documented. To facilitate the use of near miss data, it is necessary to formally encourage a culture of reporting near misses within the organisation, and to integrate such reporting as a formal element of the Quality System, similar perhaps to how deviations are reported.

The capturing of near miss events is generally not a formal activity in the pharmaceutical GMP environment at this time, and to date, little work has been done on analysing data on close calls, incidents and mishaps in order to identify unforeseen complex interactions within complex systems. The current drive towards the development and use of more formalised Quality Risk Management activities within the pharmaceutical GMP environment presents an ideal opportunity for the industry to begin formalised programmes of capturing and analysing data on near miss events. Such work, together with the application of Human Factors Engineering methods to analysis near-miss events, will likely be useful in order to identify root causes of potential major accidents, and suitable corrective actions for the prevention of such accidents.

Another strategy that NASA uses to address the risk associated with system complexity and coupling is to encourage system designs that limit system complexity and coupling

from the outset. Decoupling and reducing system complexity can be a useful risk mitigation strategy in pharmaceutical GMP environments, because manufacturing and related work processes are often multi-step and can be very complex and tightly coupled.

Change control activities, for example, relating to medicinal product packaging and artwork can sometimes be highly complex, because they can require the input of several different groups and people for the co-ordination, assessment, review, approval and implementation of the proposed change, not to mention the input of regulatory agencies and off-site printing companies as well. In addition, such activities are often tightly coupled, as there can be strict timelines to be adhered to for each part of the process, and complex interactions may have to take place in a certain order to allow the change to be implemented in a compliant but economically viable manner. Such interactions may include those between regulatory affairs and marketing groups, and between regulatory affairs and production personnel, in order to communicate and schedule product manufacturing activities with the changed packaging or labelling component.

This is an area that experience has shown to be high risk for companies. In the author's experience as a GMP Inspector at the Irish Medicines Board, many non-compliances have come to light over recent years (2005-2007) in the areas of product packaging and labelling, and these were attributed to the poor management of changes in packaging and artwork components. This has resulted in the cessation of batch release activities in several companies during 2005-2007, and in market shortages of important medicinal products. Investigations during this time have revealed that often, the procedures and systems in place at the concerned companies for packaging and artwork change control were highly convoluted, had many interdependencies, were subjected to tight timelines, and could be described as being complex and tightly coupled. Sometimes, there was a poor understanding of how the change control system operated at the companies concerned, and in one 2007 case, it emerged that key staff involved in packaging and artwork-related change control activities were totally unaware of two other key groups at another location within the same company that were highly involved in the implementation of such packaging and artwork related changes. It was clear that a reduction in system complexity and coupling would be of benefit.

- ***Example of Best Practice in this Quality Risk Management Methodology:***

  In Step 7 of the Quality Risk Management methodology developed in this work, during Risk Control activities, there is provision made for the need to consider reducing system complexity and coupling, especially after other reasonable risk control measures may have failed to reduce or control the risk(s) in question to acceptable levels.

While the above observations and strategies in relation to Normal Accident Theory are interesting, in the general pharmaceutical manufacturing environment, there is often little attention given at this time to understanding (beyond a conceptual level) the theories behind how accidents occur, especially Normal Accident Theory (90, 150). Thus, the potential existence of complex, tightly coupled systems is not one which is generally focussed on (or probably well understood in the GMP environment), and opportunities for improvement and learnings in this area are often not realised.

At the Irish Medicines Board, it has been found that an understanding of system complexity and coupling can be achieved via the use of rigorous process mapping exercises, which have allowed system complexities and couplings to be identified and documented in an easy to understand, visible manner. Process mapping exercises can also help to prioritise Quality Risk Management activities appropriately, to ensure that risk mitigation strategies developed for the process under study are not invalidated by unforeseen system characteristics, complexities and couplings later on. During a 2006-2007 developmental study carried out within the Market Compliance Section at the Irish Medicines Board, (a Section within the IMB Inspectorate managed by the author), two of the Section's main work programmes (the Sampling and Analysis programme, and the Quality Defect and Recall programme) were rigorously analysed via formal process-mapping studies. This was in order to identity potential process improvements and opportunities for efficiency gains.

During the above process-mapping work, the IMB Sampling and Analysis process was found to be highly complex and tightly coupled, with many steps, a high number of process hand-overs between staff, and many time-based interdependencies. It became evident following analysis of the process maps that the delays and backlog problems

which had been associated with the Sampling and Analysis programme in recent years could be directly attributed to the highly complex and coupled design of the Sampling and Analysis process. One delay or unforeseen event in one part of the process, such as a delay in obtaining registered analytical methods and specifications for a product, often had a significant impact on the whole programme, and the testing of samples often had to be re-scheduled as a result. With the help of an external consulting company, and as part of a business process re-engineering project, a major piece of work was carried out to re-design the process underpinning the Sampling and Analysis programme. Through this work, much of the complexity of the process was removed, due to re-design and simplification efforts both in the process steps and in the process procedures and other documentation. In addition, key process couplings such as the time-dependent links between product sampling activities, the obtaining and review of analytical methods, and laboratory capacity issues were removed. This allowed for greater flexibility in carrying out these activities, and more planning and scheduling of laboratory capacity was now made possible. The resulting re-designed process has proven to be much more efficient, and the problems of delays in sampling and analysis work, and issues with backlogs, have now been completely eliminated.

The current drive towards the use of more formalised Quality Risk Management activities in the pharmaceutical GMP environment presents an opportunity for the industry to begin identifying which systems are complex and tightly coupled. This is so that Quality Risk Management efforts may then be directed at the most highly complex and highly coupled systems. See Section 8.5 in Chapter 8 of this thesis for a recommended action in relation to dealing with system complexity and coupling issues in the pharmaceutical GMP environment.

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7.3 The Approach to Risk Management in the US Nuclear Power Generation Industry

In the United States, formal Risk Management methodologies have been used in the nuclear power generation industry since the early 1970s, and this has predominantly been achieved through the application of Probabilistic Risk Assessment methodologies (described above and in further detail below). This has resulted in the identification of design and control enhancements at nuclear power plants in the US, leading to improvements in safety, and in a reduction of the risk posed by major accidents at nuclear power plants.

By 1985, there was enough official confidence in the safety of US nuclear power plants that the US Nuclear Regulatory Commission (hereafter referred to as the NRC), in a policy statement on severe accidents in nuclear power plants, stated that "based on the available information, existing plants pose no undue risk to the public health and safety, and that there is at present no basis for immediate action or generic rule-making or other regulatory requirements" for US nuclear power plants" (58).

As is demonstrated in the Sections below, the literature and official NRC publications show that the promotion and use of formal Risk Management methodologies at the NRC was a major component in reaching this level of safety assurance.

Probabilistic Risk Assessment (PRA) has been the Risk Management method of choice in the US nuclear power industry for over three decades. The prominence of PRA in that industry is demonstrated by its place in the US legislative framework governing the nuclear industry. In August 1995, for example, the US Federal Register contained a final policy statement from the NRC in relation to the regulation of US nuclear power plants, which indicated that the NRC intended to use Probabilistic Risk Assessment methods in its regulatory activities (153).

This 1995 policy statement was important from a Risk Management perspective, because it indicated a strong move at the NRC towards an increased use of PRA, and it mandated that the use of PRA-related technologies should be increased in all regulatory matters.

7.3.1 The development and use of Probabilistic Risk Assessment methods by the US Nuclear Regulatory Commission

The origin of the use of Probabilistic Risk Assessment methodologies in the nuclear power industry goes back to the 1970s, when the benefits of using such methodologies were firmly established with the execution of a pivotal study known as the *Reactor Safety Study*, carried out between 1972 and 1975 (103). This was the first documented, formal and comprehensive application of PRA in the nuclear arena, and its results had major implications for how the US nuclear power industry would be regulated in the decades that followed.

The Reactor Safety Study, which was sponsored and initiated by the US Atomic Energy Commission but which was completed by the newly established *Nuclear Regulatory Commission* (NRC), investigated using probabilistic risk assessment methodologies (PRA) the probabilities and consequences of severe reactor accidents in two commercial US nuclear power plants.[13] Since that time, the nature of the PRA methodologies used within the US nuclear power industry has evolved and advanced significantly, particularly with the evolution of advanced computational techniques and the exponential increase in the available computer power over the last 30 years (89, 60, 62).

Following the completion of the Reactor Safety Study, research efforts were intensified at the NRC to improve the ability of its staff to assess the risks posed by severe accidents in light water reactors, and development work began on advanced methods for assessing the frequencies of such accidents. At the same time, the NRC began to gradually introduce the use of PRA into its regulatory process.

In 1979, the nuclear plant accident which occurred at the Three Mile Island US nuclear facility in Middletown, Pennsylvania on March 28, 1979, and which led to a partial meltdown of the reactor core, resulted in strong recommendations from the two official investigating teams (the so called Kemeny and Rogovin teams) for a dramatic increase

[13] Note: In the nuclear and other literature, PRA is often cited as both *Probabilistic Risk Analysis* and *Probabilistic Risk Assessment*. In this thesis, and in line with common practice, the acronym PRA is taken to stand for Probabilistic Risk Assessment.

in the use of PRA methods by NRC staff. The intention behind these recommendations was that the use of PRA methods would complement the "traditional, non-probabilistic methods" used by the NRC when analysing nuclear plant safety (154-155). The Kemeny and Rogovin recommendations did result in a rapid expansion of the use of PRA at the NRC (82).

Of the two official investigations into the Three Mile Island accident, the Rogovin report (155) had the biggest impact on the future of Risk Management activities in the US nuclear power industry, for it recommended changes in NRC policy in two important respects. Firstly, the Rogovin report recommended that the NRC should begin to specifically assess the risk of "multiple system failures" when licensing US nuclear reactors. Secondly, it recommended that the NRC should determine "probabilistic safety goals" to help define the level of plant safety that was "safe enough." (155)

These post-Three Mile Island recommendations were translated into NRC policies during the 1980s, and to support such policies, general procedures for performing PRAs were developed and published (57). In addition, the NRC developed guidance for its staff on how severe accident risks were to be assessed, and safety goals were defined against which these risks could be measured (156). At the same time, during the 1980s, technology advancements allowed for the development of a new computational model for severe nuclear accident processes, and at NRC, this led to improved PRA methods for analysing the physical processes of severe nuclear plant accidents. By the late 1980s, approximately 40 US nuclear reactors had been assessed using PRA methodology (157).

In 1988, the use of PRA in the US nuclear industry was further strengthened with what became known as the NRC's *Generic Letter* (59). This was an official NRC Directive to all US nuclear power reactor license holders, requiring that formal individual nuclear plant examinations be performed by those license holders. These *examinations* were intended to identify "plant-specific vulnerabilities to severe accidents", that could be fixed with low cost improvements (59). This directive outlined the benefits of performing such examinations, and it cited past experience with the use of plant specific probabilistic risk assessments. While the NRC did not actually mandate the

methodologies by which those individual plant examinations were to be performed, probabilistic risk assessment was one of the approaches promoted by the NRC in the above Directive.

7.3.2 The components making up the Probabilistic Risk Assessment methodology used by the Nuclear Regulatory Commission

Similar to the application of PRA at NASA, the use of PRA at the NRC, both in the early 1970s and up to the present day, has involved the use of several different component methodologies. These included quantitative Event Tree Analysis, quantitative Fault Tree Analysis techniques as well as other methods, such as Human Reliability Analysis, to determine the risk posed by nuclear plant failures.

Using these tools, potential nuclear accidents were analysed by breaking the accidents down into simpler, basic events, such as hardware component failure events. This approach sought to determine specific accident initiating events and their frequencies, taking into account the control systems that were in place at the nuclear plants under assessment, and their likely failure rates. Accident pathways of different probabilities were thus determined.

Human Reliability Analysis, described by Pyy in 2000 (106), was used as a tool in such PRA applications, in order to analyse how human error may contribute to nuclear plant accidents. Two types of potential human errors are normally considered: pre-accident errors, such as the mis-calibration of an item of equipment, and post-accident errors, such as the failure to diagnose and respond appropriately to an accident.

As explained by Rasmussen in 1981, actuarial data analysis may also be performed when determining nuclear accident probabilities, especially for cases where there may be substantial recorded experience with failures in the particular item under study (82). However, Rasmussen stresses that a cautious approach should be taken with respect to the use of such historical data, as changes in accident rates over time, and changes in technologies, can greatly influence the validity of such historical data.

With respect to the use of quantitative Event Tree Analysis and quantitative Fault Tree Analysis at the NRC, their use of these methodologies was primarily based on the *Bayesean* (or subjectivist) approach to calculating probability distributions (82). This was an approach that recognised that there was rarely enough historical data from actual observations made on a process to calculate precise probability values for uncertain events, and it provided an accepted method of calculating probability distributions. (Bayes' theorem, which provides the foundation for the Bayesean approach to calculating probability distributions, can be reviewed in any good text on probability and statistics.)

The NRC used Fault Tree Analysis to predict the expected probability of failure of a system in the absence of actual experience of failure (82). This occurred when there was very little operating experience with the item of interest, or when the system failure rate was so low that no failures had yet been observed. Fault Tree Analysis became especially applicable when the system was made up of many parts, and when the failure rate of the individual parts was known (82). Individual part/component failure rates were used to assign primary event probabilities in the fault tree, and the probability of the top event in the fault tree could then be calculated using Boolean algebraic methods.

In the pharmaceutical GMP environment, it is difficult at this time to apply Fault Tree Analysis in the same way as it has been used in the Nuclear power (or Aeronautics) industries. In the authors experience, in the pharmaceutical GMP environment at this time, there is usually little information formally captured within a company's Quality Management System on the individual failure rates of equipment components, and, because many items of equipment are customised for the operation or process at hand, the availability of failure rate data from other sources (outside of the company) using the same item of equipment may often be limited.

In contrast, in the nuclear power industry, many of the components used in plant operating and control equipment are standard commercial items that are widely used in many similar applications in other plants, and as a result, information on the individual failure rates of those components often exists (82).

As at NASA, the NRC has used simple examples to demonstrate their application of methods such as Fault Tree Analysis. In the latter organisation, the example of a loss of power to safety systems on demand has been used to demonstrate the NRC's approach to Fault Tree Analysis (82).

7.3.3 Risk Management Re-assessments performed by the Nuclear Regulatory Commission

Another important aspect to the NRC's approach to Risk Management during the late 1980s when assessing the risk of severe accidents at nuclear power plants was the initiation of a process of performing *re-assessments* of the risks of such accidents, using updated PRA methodology and advancements in technology.

The first major re-assessment exercise that was carried out by the NRC was that published in the 1989 NRC report known as *NUREG 1150* (60, 62). This was an update on the Reactor Safety Study of 1975, and the re-assessment study involved the application of (at the time) current PRA methodologies to the two commercial nuclear power plants studied via the Reactor Safety Study, as well as three others.

The PRA methodologies used in the NUREG 1150 study had advanced significantly since the original 1972-1975 work. This was not just a result of the evolution of more sophisticated computational techniques since the 1970s, but there were advances in other key areas too.

For example, the use of *expert judgement* had been a feature of the Reactor Safety Study, but in the NUREG 1150 re-assessment exercise, more formalised and documented procedures had been employed for the elucidation and documentation of expert judgements, particularly with respect to obtaining probability distributions for uncertain parameters.

In the PRA-based Risk Assessments that were performed in the 1989 re-assessment studies, accident frequency analysis was the first step in each PRA performed. This was followed by studies into the loss of containment of radioactive materials, (step 2) the

progression of such accidents and how radioactive material would be transported following containment loss (step 3). Studies into the off-site consequences comprised the fourth step in the Risk Assessments, and finally, in step 5, risks were calculated for the accident sequences identified.

- ***Examples of Best Practice in this Quality Risk Management Methodology:***

  With respect to the accident frequency analysis that comprised the first and main step of the PRA methodology, there are several features of the Quality Risk Management methodology developed in this work that are similar to that approach.

  For example, in relation to the treatment of accident sequence initiating events, in the NRC's PRA approach, (60), such events are identified, documented and screened prior to any rigorous assessment being applied to any specific accident sequence initiating event. This screening is done on the basis of an estimated probability of the accident sequence initiating event. Here, very low frequency events are discarded without further consideration, and the accident sequence initiating events that remain are subjected to the detailed analysis that follows.

  This is very similar to the design of Step 4 of the Quality Risk Management process developed here, which requires all of the suggested potential negative events to be documented and screened prior to progressing any particular potential negative event through the remaining steps of the Quality Risk Management process. This screening is done on the basis of a consideration of the estimated severity and probability associated with the potential negative event.

  Also, in relation to controls that reduce the risk associated with particular accident sequence initiating events, in the NRC PRA approach, controls which prevent core damage (i.e. preventative controls), as well as "front-line systems" which serve to reduce the severity of the accident sequence initiating event after it has occurred, are identified and then assessed.

  This is similar to Step 5 of the Quality Risk Management process developed here, which requires the identification and critical evaluation of both occurrence-related

controls and severity–related controls for the potential negative event in question. (The occurrence-related controls are preventative in nature, while the severity–related controls can be considered to be similar to the 'front-line systems' envisaged by the NRC PRA approach, as these serve as back-up or redundancy-related controls which counteract or eliminate the negative consequences should the negative event in question occur.

The PRA re-assessment studies performed by the US NRC on the two common commercial US nuclear power plants showed interesting results and insights into the factors which can lead to different results from Risk Assessment exercises performed on the same item under study.

The NRC found different results for the probabilities of core meltdown accidents for the two common nuclear power plants which had been assessed both in the first PRA exercise of 1972-1975 and in the 1989 re-assessment exercise. (These two reactors are known as the Slurry and Peach Bottom reactors.) Lower probabilities of core meltdown were obtained in the 1989 study (60) compared with the 1975 study (103). However, as noted by Rasmussen in a review of the Reactor Safety Study, given that the uncertainty ranges in these probability values overlapped, the answers for the Slurry and Peach Bottom reactors were actually "quite close" between both studies (157).

However, with respect to the amounts of radioactivity that might be released following a core meltdown accident at the Slurry and Peach Bottom reactors, the two studies found markedly different results, with a one order of magnitude difference. The 1989 re-assessment study predicted significantly lower amounts of radioactivity being potentially released following a major core–meltdown accident than the 1975 study.) There were two main reasons attributed to these differences.

Firstly, it was recognised that the PRA exercises that had been performed in both studies were "snapshots in time", taken about 15 years apart, and during that time period, the plants had "implemented hardware modifications and procedural improvements with the stated purpose of improving safety", thus driving core damage frequencies downwards (157).

Secondly, it was recognised that significant advances had occurred in applying probabilistic analysis in nuclear power plant applications since the 1972-1975 Reactor Safety Study, as "computational techniques were now more sophisticated", and the level of detail in reactor modelling had increased enormously (157). This reduced or eliminated previous analytical conservatisms. For example, it was shown by research conducted in the US, Japan and Western Europe after 1975 that the radioactivity estimates in the Reactor Safety Study were generally too high (i.e. conservative), and that the amount of radioactivity potentially released by these plants following a major core meltdown accident was likely to be much lower. The results from these later studies were confirmed by radioactivity measurements taken at the Three Mile Island plant after the accident in 1979 (82).

Other comparative learnings were also made as a result of the 1989 re-assessment exercises. In the 1989 PRA exercises, new types of failures had been uncovered and assessed that had not been identified in the first PRA study of 1972-1975. For example, the 15 years of experience between the two PRA studies had shown that failures could occur in the reactor coolant pump seal, and this not been known at the time of the Reactor Safety Study. In addition, intersystem dependencies (similar to the system couplings discussed in Section 7.2.8, above) had been uncovered in the 1989 studies which had also not been known at the time of the Reactor Safety Study.

These findings demonstrate the importance of performing re-assessments on already executed Risk Management exercises, and this supports the fact that Risk Review activities were included in the ICH Q9 view of Quality Risk Management for the pharmaceutical industry.

7.3.4 The Limitations and Problems of Probabilistic Risk Assessment in the US Nuclear Power Industry

Like all Risk Management methodologies, problems of uncertainty have been experienced with the use of the Probabilistic Risk Assessment methodologies in the US Nuclear Power industry.

In the 1989 NUREG 1150 re-assessment study, for example, the final report on the study explained that the PRA exercises that had been performed were subject to the limitations of all such PRA studies, and it stated that "these limitations relate to the quantitative measurement of certain types of human actions (errors of omission, heroic recovery actions), ... failure rates of equipment, especially to common-cause effects such as maintenance, environment, design and construction errors, and ageing" (60).

With regard specifically to the uncertainty associated with the outputs of Fault Tree Analysis exercises as part of the PRA approach, the use of complex computer codes to calculate the probability distributions associated with the top failure event in a fault tree made it difficult to generate an overall uncertainty value for the top event (82). This was because one cannot propagate the estimated uncertainties associated with each basic event[14] in the fault tree up through the fault tree to the top event. The Nuclear Regulatory Commission instead used a technique called *Monte Carlo calculations* in its 1989 PRA studies to estimate such uncertainties.

In Monte Carlo calculations, a sample is taken from each of the input probability distributions, and a calculation is thus made of the probability from the sample taken. This process is then repeated several thousand times (using computer software) to produce a distribution for the top event probability from which confidence limits can be derived.

There can also be significant uncertainties associated with estimates of human errors and their failure rates during Fault Tree Analysis work. Here, failures of omission or commission are normally considered in PRA exercises utilising Fault Tree Analysis, and uncertainties in this area have been cited by the US Nuclear Regulatory Commission as an issue with PRA generally (82). In general terms, the US Nuclear Regulatory Commission has found that Fault Tree Analysis can be "exceedingly difficult" to apply to very complicated problems, particularly when a quantitative prediction of system failure is required (82). The NRC's experience has been that when

[14] The terms *Basic Event* and *Top Event* are commonly used in Fault Tree Analysis work. A Top Event is the overall fault or event of interest that is under study when a Fault Tree Analysis exercise is being

the top event was selected at too high an indenture level in the system under study, (such as when the accidental release of radioactivity from a nuclear power plant is taken as the top event), the resulting fault tree became so large that it was "hopelessly complicated" and difficult to complete (82). This finding has been mirrored in the author's own research on this issue also. For a detailed discussion and for a practical case study in this regard, see the 2007 research paper published in the Journal of Validation Technology by this researcher (125).

The above problems with Fault Tree Analysis activities during Probabilistic Risk Assessment exercises led the US Nuclear Regulatory Commission towards the use of the Risk Management methodology known as Event Tree Analysis (ETA), as an extra component of its PRA range of methodologies.

Event Tree Analysis is a Risk Management tool that allows a problem to be broken down into smaller and more manageable parts, to which Fault Tree Analysis may then be applied. The logic used in Event Tree Analysis is practically the reverse of that used in Fault Tree Analysis. In the latter, one starts with an undesirable (top) event and reasons back to determine how it might have happened.

In Event Tree Analysis, one starts with an initial event and asks 'to what states of the system the initial event might lead?' Here, the safety and other control systems that may be in place for overcoming the effects of the undesirable event (called an *initiating event* in ETA terminology) are assessed in terms of their probabilities of success or failure. Accident pathways are then generated for the different failure scenarios, and the overall probability associated with each accident pathway or scenario is determined on the basis of the individual probabilities assigned to each control mechanism success or failure event. These individual probabilities are determined using Fault Tree Analysis. (This is similar to NASA's use of Event Tree Analysis and Fault Tree Analysis in PRA studies, as described earlier in this Chapter.).

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performed. It is connected by logical gates in the fault tree to component failures known as Basic Events.

The idea behind this approach is that a fault tree is generated to identify potential causes for the failure of each control mechanism listed in the event tree. Once the basic, primary failure events are identified from the fault tree, their probabilities are estimated on the basis of known component failure rates or other data, such as Human Factors Engineering principles, if the failure of concern is related to human error. Computer software is then used to calculate the probability of occurrence of the top event in the fault tree, which becomes a *control failure probabilities* in the event tree. In this way, it becomes possible to assign probabilities for each of the accident scenarios in the event tree.

Like Fault Tree Analysis, Event Tree Analysis is not without its limitations and problems. As described by Rasmussen (82), one challenge with ETA is to "define a set of initiating events that, when fully developed, produces all the important accident sequences." At nuclear power plants, this is not such a problem, because as Rasmussen indicated, every risk scenario is associated with one event only, serious overheating of the reactor fuel (82). This was probably an over-simplification of the situation, however, and it is likely that such statements were one reason for some of the criticisms that followed the publication of the Reactor Safety Study report in 1975 (158, 159).

Another problem with Event Tree Analysis experienced by the NRC related to the order of placement of the individual control functions across the top of the event tree. These control functions are regarded as *barriers* to the progression of various accident pathways, and their order of placement along the top of the event tree becomes important when the performance of one control system affects the performance of another control system.

The Atomic Energy Commission, which sponsored the original Probabilistic Risk Assessment exercises during the Reactor Safety Study of the 1970s, struggled with this problem, and they found that it was essential for the analysts performing the PRA exercises to "have a detailed understanding of all plant systems" and how they operated and interacted with each other (103). The Atomic Energy Committee found that a number of iterations to produce a tree that handled this problem had to be developed,

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See Reference No. 33 for more information.

and that the formal interaction of several analysts from different areas of expertise was required in order to produce the final event tree (82).[15]

7.3.5 The evolution of a 'Risk-Informed' Environment in the US Nuclear Power Industry

In a useful review of the use of Risk Management in the US Nuclear power industry, Coburn and Weedle (159, 160) made a number of interesting points in relation to the potential use of Risk Management methodologies in the life sciences industry, which includes the pharmaceutical GMP-regulated industry. They focused particularly on what the life sciences industry might learn from the experiences of the US nuclear power industry in this regard.

Coburn and Weedle described how, in the US nuclear power industry, the many years of experience with using and optimising PRA-based Risk Management methodologies within both the regulatory setting and commercial industry have resulted in the gradual development of what is known as a *risk-informed* environment, rather than a *risk-based* environment. This *risk-informed* environment is described as a "middle ground". Here, deterministic concepts such as *safe* and *unsafe* are no longer used; rather, there is now the concept of "*safe enough, or not (159)*".

Deterministic, or rule-based, regulations do still exist in this risk-informed environment, but these are now formally and officially accompanied by the flexibility and scope of risk-based concepts and methodologies, such as PRA and other Risk Management tools. Importantly, in the risk-informed environment, the Risk Management approaches and tools in use within the industry are known to, and officially endorsed by, the regulators of that industry. Thus, in the risk-informed environment, "risk assessments augment, rather then replace", the existing regulatory structure, and the methods by which this occurs are officially accepted by both regulators and industry alike (159). A real life example of this working in practice is the Standard for Probabilistic Risk Assessment for Nuclear Power Plant Applications, (161), published by the American Society of Mechanical Engineers in April 2002, which was endorsed by the US Nuclear

[15] This is an example of why multi-disciplinary teams are useful during Risk management exercises.

Regulatory Commission in February 2004, via publication of the NRC's Regulatory Guide No. 1.200 (61).

Risk-informed thinking was given official standing in the US nuclear power industry in November 2002, with the publication of the NRC's Regulatory Guide 1.174 titled '*An Approach for Using Probabilistic Risk Assessment in Risk-Informed Decisions on Plant-Specific Changes to the Licensing Basis*' (162). In this Guide, the NRC acknowledged the degree to which Probabilistic Risk Assessment had become part of the decision-making process for operating and regulating the nuclear industry. It stated that "during the last several years, both the NRC and the nuclear industry have recognised that PRA has evolved to the point that it can be increasingly used as a tool in regulatory decision-making". Furthermore, Regulatory Guide 1.174 went on to give detailed guidance on how industry should actually apply PRA methodologies when assessing proposed plant changes (162).

At a practical level, in this new risk-informed environment, participants (such as nuclear reactor operators and NRC regulatory staff alike) are permitted to consider risk when making key decisions, such as when assessing plant change control-proposals (162). However, coupled with this freedom to make risk-based decisions, are explicit rules which must still be followed while doing so, and this is a principle feature of the risk-informed environment. For example, the *deterministic* constraint of having clear and formal requirements in place for staff training activities on any risk management methodology in use still exists. There is also a *deterministic* requirement to consider all risk variables for the regulatory application in which any particular risk assessment technique is used, and to apply risk models consistently (162).

This approach also gives nuclear plants the ability to continuously improve their safety controls, but on a risk-basis, while at the same time satisfying the sometimes conservative needs of regulators for clear and definite regulations to be in place for the generation of nuclear electricity. As Coburn and Weedle point out (160), this environment is beneficial in that it assures the public that there are regulatory controls in place governing "risky" activities such as the generation of nuclear power.

While the above risk-informed, Probabilistic Risk Assessment-based approach is perhaps at the cutting edge of Risk Management applications at this time, it may not be directly transferable to the pharmaceutical manufacturing industry at the present time. This is because, given the highly quantitative nature of PRA-based methodologies, and the significant differences between the nuclear power and pharmaceutical manufacturing industries (for example, in terms of the number of differing production processes which are a feature of the pharmaceutical industry but not the nuclear power industry), PRA-based methodologies may be "too complex, time-consuming and costly" to be practical for assessing risks inherent in multiple pharmaceutical production processes (160).

There are elements of this PRA-based approach, however, that can easily be adopted by the pharmaceutical industry at this time, and these would likely lead to improvements in the application of Quality Risk Management there. These include:

- The formal evaluation of controls that prevent or mitigate against an accident sequence before the probability of that accident sequence occurring is determined.

- The use of Fault Tree Analysis as an integral part of the potential negative event or failure mode identification process.

With respect to the former, this is a useful feature of the nuclear PRA approach. Here, the expected performance of each control is critically evaluated at an early stage in the Risk Management process, and this information is used when the probability of the concerned accident sequence occurring is calculated, thus reducing the level of uncertainty associated with those calculated probability values. This is achieved using a combination of Event Tree Analysis and Fault Tree Analysis, but is seldom a feature of the Quality Risk Management tools commonly used in pharmaceutical manufacturing industry, such as FMEA. It is likely that there are benefits to be gained by adopting such an approach in that industry.

With respect to the latter, as outlined above, in PRA-based approaches, Fault Tree Analysis is used in order to determine the causes and probabilities of control system

failures during possible accident pathways. Fault Tree Analysis can likewise be applied during Quality Risk Management exercises in the pharmaceutical GMP environment to help identify potential negative events and their causes. As a practical demonstration of this, the reader is referred to the detailed Case Study presented in the author's research paper published in the Journal of Validation Technology in February 2007 (125).

- ***Examples of Best Practice in this Quality Risk Management Methodology:***

  A central feature of the Quality Risk Management methodology developed in this research work is the formal and critical evaluation of GMP controls during Steps 5, 6 & 7 of the Quality Risk Management process. This is carried out for each potential negative event, both before risks are estimated and afterwards, during Risk Control activities, (if the latter are required).

  Thus, at Steps 5, 6 and 7 of the Quality Risk Management process, both current and proposed controls are evaluated for their risk mitigating potential with respect to the potential negative event under consideration, and this is a key activity prior to the assigning of the Probability of Occurrence, Severity or Detection ratings for the potential negative event at hand.

  Furthermore, at Step 8 of the Quality Risk Management process, the qualification, validation, documentation and training requirements for each GMP control are identified and documented, regardless of whether the control is already in place or not. This contrasts with many of the currently available Quality Risk Management methodologies, which usually only consider (if indeed they do so at all) the qualification, validation, documentation and training requirements for <u>new</u> controls identified to mitigate risks, not currently-in-place controls.

Coburn and Weedle promote the evolution of a "middle ground" for the application of Risk Management methodologies within the life sciences industry (160). This *middle ground* will likely take time to develop, and they contend that the pharmaceutical industry will very likely follow the experience of the nuclear power industry in this regard, which took approximately 25 years to reach the *risk-informed* state of affairs described above.

They propose that the end goal for the pharmaceutical industry should be that the industry will be in a position at some point in the future to "quantify business risks in predictable ways without resorting to methods that are unaffordable." In relation to equipment qualification, for example, one way this approach could be used would be to "set quantitative thresholds" for defining direct or indirect effects and critical or non-critical functions (160).

7.3.6 The Concept of 'Defense in Depth' in the US Nuclear Power Industry

One final feature of the application of Risk Management methodologies in the US nuclear power industry that is of relevance to this comparative review is the NRC's regulatory requirement to consider what are known as *defense in depth* control strategies during the operation of nuclear power plants (61).

As Coburn and Weedle point out, *defense in depth* is a 'regulatory philosophy' adopted by the US Nuclear Regulatory Commission, which holds that multiple means to accomplish safety functions must be provided, so that no one measure should be relied upon to ensure the safety of the plant (160). In November 2002, the US Nuclear Regulatory Commission, in its Regulatory Guide No. 1.174 (162), explained how the '*Defense in Depth*' philosophy applied to change control at US nuclear plants. Here, defense in depth was described as "a means to accomplish safety functions and prevent the release of radioactive material" and as an effective way to account for uncertainty in equipment and human performance (162).

The NRC Regulatory Guide No. 1.174 went on to introduce the concept of *risk balancing* within defense in depth programmes. It explained that the extent of defense in depth may be determined by a comprehensive risk analysis, where "a reasonable balance is maintained" between the prevention of core damage, the prevention of containment failure, and consequence-mitigation activities (162).

This is similar in some respects to the *Risk Balancing* approach employed by NASA within its so called 'knowledge-based decision making environment', discussed in detail earlier in this chapter (139). At NASA, risk is viewed as a resource that can be traded

and balanced between the sub-systems of the item under study, as long as there is sufficient risk mitigation in place, for example via component redundancy measures, to mitigate against risks which are not reduced below acceptable levels.

- ***Examples of Best Practice in this Quality Risk Management Methodology:***

  The Quality Risk Management methodology developed in this research is similar in several respects to the NRC's balanced 'defense in depth' approach described above. This is because this methodology formally recognises, via Steps 6 and 7 of its Quality Risk Management process, that it is not always necessary to reduce all risks below a certain risk threshold before they can be accepted, as long as there are controls (i.e. risk mitigation strategies) in place which mitigate against that risk, should the negative event which might lead to it occur.

  Indeed, this feature is reflected in one of the fundamental principles underlying the methodology - Principle No. 5, as discussed in Section 2.3.1.1 of Chapter 2 of this thesis. This Principle holds that there may be some risks which cannot be eliminated or reduced to an acceptable level with current or realistic controls/resources, but which may be controlled to an acceptable level with improved detection or other measures.

  In addition, this methodology also makes clear provision for, and actually promotes the putting in place of, recovery or redundancy-based controls, via Steps 5 and 7 of the Quality Risk Management process, and this is similar to the NRC's multiple defense control approach discussed above.

Notwithstanding the above examples of best practice, it is evident that, in the pharmaceutical GMP environment, Quality Risk Management concepts and methodologies are still at their early stages of development and adoption. Formal defense in depth strategies, for example, such as those described above for the Nuclear power industry, or the risk balancing approaches used by both the NRC and NASA, have not yet been developed to any significant degree in the pharmaceutical GMP environment. In this researcher's opinion, Quality Risk Management concepts and methodologies in the pharmaceutical GMP environment are nowhere near the level of

development or sophistication that has been achieved by NASA and the US Nuclear Regulatory Commission in their respective regulated environments.

In the US nuclear power environment, for example, the US Atomic Energy Commission and later the US Nuclear Regulatory Commission were the actual technical and administrative drivers behind the development and application of the highly sophisticated *Probabilistic Risk Assessment* (PRA) Risk Management methodologies in that environment. The resulting level of technical detail in NRC Regulatory Guides on the nature and practical application of PRA-based Risk Management methodologies demonstrates how advanced the US Nuclear Regulatory Commission, as a regulatory body, is in understanding those Risk Management methodologies.

Consider the aforementioned NRC Regulatory Guide of November 2002, titled '*An Approach for Using Probabilistic Risk Assessment in Risk-Informed Decisions on Plant-Specific Changes to the Licensing Basis*' (162). This provided detailed guidance to the US nuclear power industry on the different types of uncertainty (*aleatory* uncertainty and *epistemic* uncertainty) which should be addressed and quantified in PRA Risk Management reports, and methods for the analysis of such uncertainties were also given. In contrast, within the EU GMP environment, as of December 2007, the only official guideline available for regulators and industry alike on the application of Quality Risk Management methodologies was ICH Q9, published in November 2005 (9). Furthermore, this provided only high level, conceptual and non-technical guidance on the subject, and there is no technical or other guidance presented on how to deal with key issues such as uncertainty during Quality Risk Management work.

The above example is not an isolated case. The NRC's Regulatory Guide of February 2004 (61), titled '*An Approach for Determining the Technical Adequacy of Probabilistic Risk Assessment Results for Risk-Informed Activities*', further demonstrates the level and depth of technical understanding within the US regulatory body with respect to Risk Management methodologies. This Guide provided specific and practical guidance to the industry and its regulators on the "functional requirements of a technically acceptable PRA" report (61). For example, it provided detailed information on the general technical elements that are necessary for what is called a *Level 1 PRA* (this is a PRA Risk Management exercise that studies the frequency of

core-damage accidents) and a *Level 2 PRA* (which studies both core damage accidents as well as the early release profile of radioactivity following a core damage accident in a nuclear power plant). Again, this is in sharp contrast to the current level of technical development and expertise within EU GMP regulatory bodies in the area of Quality Risk Management, where no detailed official regulatory guidance has been developed for either inspectors or industry on the required technical content of Quality Risk Management reports or studies for any particular GMP application.

This is not surprising, as it must be understood that ICH Q9 was only finalised in late 2005, and as result, the EU GMP environment is still at the early learning phases in its adoption of Quality Risk Management approaches. Further discussion in this regard is presented in Chapter 8.

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Chapter 8

Conclusions & Recommendations

8.1 Introduction

This research work was concerned with investigating the risk-based regulatory requirements that are currently in place in the European Union governing the manufacture of medicinal products, and developing a practical solution designed towards meeting a particular set of those requirements.

The main goal of this research work was to develop a Quality Risk Management methodology that served as a practical solution for facilitating compliance with the aforementioned Annex 15 GMP requirements, and which was fully in line with the principles and guidance of ICH Q9, on Quality Risk Management.

As documented in Chapter 1 of this thesis, three main research objectives had been defined at the outset of this work.

The **first and primary objective** of this research was to develop a Quality Risk Management methodology that was designed to facilitate compliance with the risk-based Qualification, Validation & Change Control GMP requirements of the EU. The research methods and results associated with this research objective were presented and discussed in Chapters 2 through 5 of this thesis.

The **second objective** of this research was to develop a practical and detailed training programme on the use of this Quality Risk Management methodology, which provided comprehensive training materials for facilitating training activities, as well as a documented strategy for the provision of training in a timely and resource-efficient manner. The research methods and results associated with this research objective were presented and discussed in Chapter 6 of this thesis.

The **third objective** of this research was to carry out a benchmarking exercise, in which the approach to Quality Risk Management developed in this work would be compared, in terms of best practice, with the application of Risk Management in two industries that can be considered to be mature and advanced in their use and application of Risk Management.

The US Aeronautics Industry, as represented by the work of the National Aeronautics Space Administration (NASA), and the US Nuclear Power Generation industry, as represented by the work of the Nuclear Regulatory Commission (NRC), were selected for this benchmarking exercise. The results associated with this research objective were presented and discussed in Chapter 7 of this thesis.

In this Chapter, the conclusions that were drawn from the results associated with each of the above three research objectives are presented. Several recommendations for future work activities are also presented, thereafter.

8.2 Conclusions for Research Objective No. 1

There were three parts to this Research Objective, numbered *1(a), 1(b) & 1(c).* Each of these is re-stated in bold, italicised text below, and the conclusions drawn from the results pertinent to each are thereafter presented.

8.2.1 Conclusions for Research Objective 1(a)

Research Objective No. 1(a) was as follows:

The methodology should be in line with the principles and guidance of ICH Q9. Thus, the evaluation of risk by the methodology should ultimately link back to a potential harm to the patient, and the level of effort, formality and documentation provided by the quality risk management process should be commensurate with the level of risk. Also, the methodology should serve as a readily usable, documented and complete Quality Risk Management solution, without requiring extensive modification before it may be used to address all of the elements of Quality Risk Management as defined in ICH Q9.

The Quality Risk Management methodology developed in this research work is fully in line with the principles and guidance of ICH Q9. The final version of ICH Q9 stated that two primary principles of quality risk management were a) that the evaluation of the risk to quality should … ultimately link to the protection of the patient, and b), that

the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

Both of these ICH Q9 principles were fully reflected in the design of the Quality Risk Management methodology developed here. As discussed in Chapter 2, for example, when the initial version of this methodology was being developed, a set of twelve fundamental principles was defined to direct and guide the design and development of the methodology. One of those principles, Principle No. 8, stated that "... while the concerns of all involved stakeholders should be taken into account in any Quality Risk Management exercise, protection of the patient is of prime importance, and therefore, Quality Risk Management should ultimately link to the protection of the patient."

Several of the other fundamental principles also had a patient emphasis, such as Principle No. 2, which included the term *harm* in the definition of risk used by this methodology, and which indicated that harm was not only considered to be damage to health, but it also included the damage which could occur from loss of product quality or availability. These Principles were in line with the aforementioned points made by ICH Q9.

As discussed in Chapter 6, the above fundamental principles were not mere aspirational statements made at the beginning of this research work; they were formally incorporated into all aspects of the design of the Quality Risk Management process and the associated explanatory guidance material that were developed for this methodology.

With regard to the ICH Q9 principle that the level of effort, formality and documentation associated with the quality risk management process be commensurate with the level of risk, this principle has also been fully reflected in the design of this methodology. For example, as Step 4 of the Quality Risk Management process indicates, this methodology represents a highly formal and rigorous approach to Quality Risk Management, and it requires effort, training and the completion of a highly detailed ten step Worksheet in order to fully execute Quality Risk Management exercises using it.

In addition, in this methodology, only the highest priority/most important potential Negative Events should normally be selected for formal evaluation by the methodology. Step 4 of the process provides a detailed screening process to facilitate this. In this way, the methodology is applied to the most complex and most critical processes, systems, concerns or issues, so that its use is commensurate with the level of risk.

With regard to the requirement in Research Objective 1(a) that the methodology should serve as a readily usable, documented and complete Quality Risk Management solution, without requiring extensive modification before it may be used to address all the elements of Quality Risk Management as defined in ICH Q9, these were also key considerations during the design and development of the methodology. Thus, the Quality Risk Management process used by the methodology, and the Worksheet which gives effect to that process, reflect all of the aforementioned elements of Quality Risk Management as outlined in ICH Q9. As discussed in Chapter 6, no modification is required to either the process or the worksheet before they may be used to execute the full Quality Risk Management process as outlined in ICH Q9.

The Worksheet is a highly structured, practical and ready-to-use component of the methodology, and it reflects all of the key points of each of the ten steps which make up the Quality Risk Management process used by the methodology. The many practical Case Studies, problem scenarios and workshops that were used to test and optimise the structure of the design of Worksheet are testament to this fact.

8.2.2 Conclusions for Research Objective 1(b)

Research Objective No. 1(b) was as follows:

The methodology should have wide applicability across a broad range of areas within the GMP-regulated environment as a solution for determining, on a risk basis, the scope and extent of validation and the likely impact of changes.

From the results generated by the series of case study and workshop testing activities that were performed on the methodology during its various stages of development, it

can be concluded that the methodology is widely applicable across a broad range of areas within the GMP-regulated environment, as a solution for determining, on a risk basis, the scope and extent of validation and the likely impact of changes.

As discussed in detail in Chapter 6, this was demonstrated in part by the successful application of the methodology across a broad spectrum of GMP areas and activities, including Change Control proposals, for which, in each case, new qualification and/or validation requirements, or other additional actions, were identified that had not been identified prior to the execution of the Quality Risk Management exercise. The GMP areas and activities to which the methodology was applied during this work are described in Chapter 6.

In all cases, the qualification and/or validation requirements, and the other additional required actions, were directly related to the risks that had been identified during the Quality Risk Management exercises.

In addition, a number of specific and important aspects of the methodology, such as the way in which the methodology deals with risk detection issues, and the way in which GMP controls are classified during Steps 5 through 7 of the Quality Risk Management process, were further studied when assessing the level of applicability of the methodology. This was in order to determine how well those aspects of the methodology applied to a range of different situations, problems and scenarios.

The situations, problems and scenarios investigated are described in Chapter 6, and in all cases, it was found that the methodology performed precisely as intended, in relation to how risk detection issues were dealt with, and in relation to how GMP controls that were pertinent to the failure or problem at hand were classified.

Overall, it is concluded that the methodology is applicable to a wide range of product types, across a range of materials and dosage forms, and to a diverse range of different GMP-related activities. In addition, both retrospective and prospective applications were easily facilitated by the methodology, as were formal Change Control proposals.

The wide applicability of the methodology was further (indirectly) demonstrated by the high level of external industry interest in the methodology that has been observed. This interest has come from a number of different companies and individuals, including pharmaceutical manufacturing companies, pharmaceutical consulting and training companies, and a multinational medical devices manufacturer headquartered in the US. In this regard, several pharmaceutical manufacturing companies have started using the methodology in their day-to-day work activities, as a means of formally applying Quality Risk Management principles to key areas of concern within their Quality Management systems.

In the period 2006-2007, for example, the author became aware of three multinational pharmaceutical manufacturing companies that had adopted this methodology as their main approach to Quality Risk Management. One of those companies publicly acknowledged this during a presentation on Risk Management given by that company at the 2007 annual *Qualified Person Forum* meeting hosted by Trinity College, Dublin, during May of that year (163). The other two companies communicated their use of the methodology to the author privately.

In addition, one UK-based pharmaceutical consultancy & training company advised the author in mid-2007 that during Risk Management training seminars run by that company internationally, this methodology is referred to, and that there were plans in the near future to begin using the methodology with their client companies (129).

Interest in the methodology has also come from some unexpected parties. A research team located within the School of Pharmacy at the University of Vienna, for example, contacted the author in early 2007 to request permission to apply the Quality Risk Management methodology to support the validation of a scaled-up active pharmaceutical ingredient synthesis process developed at the University of Vienna (164). The validation of this process is scheduled to take place during 2008.

8.2.3 Conclusions for Research Objective 1 (c)

Research Objective No. 1(c) was as follows:

The methodology should offer a Quality Risk Management solution that is value-adding, not only in facilitating compliance in the GMP-regulated environment with the risk-based qualification, validation and change control requirements of the EU GMP Guide, but also in facilitating Quality Risk Management training and educational activities.

This methodology was specifically designed for application within GMP environments, as a practical and systematic means of determining, on a risk-basis, the scope and extent of validation, and the likely impact of changes across a broad range of GMP-related areas and activities.

Detailed and practical examples of the usefulness of the methodology in achieving risk-based qualification and validation are presented in Chapters 2 through 4 of this thesis. An overview of the areas, problems and scenarios to which the methodology was applied is presented and discussed in Chapter 6, and as demonstrated above in Section 8.2.2, this methodology has wide applicability across a broad range of areas within the GMP-regulated environment.

In relation to Change Control, which is a significant activity for GMP environments, as discussed in Chapter 6, a Change Control procedure can sometimes serve as a Quality Risk Management approach in its own right. However, this research found that when a formal and separate Quality Risk Management methodology was applied to Change Control proposals, there was more of an opportunity to take an objective step back from the proposed change, so that a more comprehensive and rigorous evaluation of the potential risks presented by the proposed change could be made. This was confirmed in each of the Change Control-related case studies and workshops that were developed and run using this methodology, where risks were identified during the Quality Risk Management exercise that had not been identified prior to the execution of those exercises.

Another advantage of this approach was that, while it is true that Change Control procedures often assess the impact of the proposed change on areas such as validation, documentation, training, cleaning, etc., from the author's experience, they often fail to look at the bigger picture, and sometimes neglect to ask the key question from a Quality Risk Management perspective, which is simply '*What can go wrong if this change is implemented*?' This research work demonstrated that the application of a separate and formal Quality Risk Management methodology to important Change Control proposals can ensure that such considerations are not overlooked, before the proposed change is approved and implemented.

As noted earlier in this Chapter, this methodology was designed to serve as a complete Quality Risk Management solution for GMP environments, addressing all of the components of Quality Risk Management as defined in ICH Q9. As discussed in Chapter 1, none of the other Quality Risk Management methodologies that are currently available was designed for such applications within the GMP environment, and as a result, they have usually required a high degree of modification in order for them to be used for such purposes.

For this research and its resulting Quality Risk Management methodology to be *value adding*, however, it was considered important during this work that the new Quality Risk Management methodology developed here should not '*re-invent the wheel*', by replicating or 're-packaging' Quality Risk Management methodologies that had already been developed.

It was also considered appropriate to acknowledge, to build upon and to take into account, where possible, some of the useful features of existing Quality Risk Management methodologies, particularly within their specific areas of application. In addition, it was considered important to make use of the knowledge and learnings gained from other fields of research and from the scientific literature in general.

The following sections present the conclusions of this research work with regard to these points.

8.2.3.1 How this methodology draws upon, and contrasts with, several existing Quality Risk Management methodologies and other fields of research

This methodology draws upon some of the useful features of several existing Quality Risk Management methodologies and approaches that are currently in use in the GMP environment. These include:

- The Failure Mode & Effects Analysis (FMEA) and the Failure Mode, Effects and Criticality Analysis (FMECA) Quality Risk Management approaches (46-47, 51)

- The Hazard Analysis and Critical Control Points (*HACCP*) Quality Risk Management approach, (48-49)

- The ISPE's Impact Assessment method for determining component criticality and related commissioning and qualification requirements for equipment and facilities (67)

- The Risk Assessment methodology for the validation of computerised systems as described in the ISPE's GAMP4 publication (55)

Numerous and detailed practical examples of this are provided in Chapter 6.

Notwithstanding the above, the methodology that has been developed in this work offers a Quality Risk Management process and an overall solution to Quality Risk Management that differs considerably from existing methodologies in many important respects. Numerous practical examples of this are provided in Chapter 6. These demonstrate that this work did not '*re-invent the wheel*', by replicating or re-packaging the Quality Risk Management methodologies and approaches that had already been developed.

This methodology adds value in that it facilitates a rigorous, comprehensive and complete application of Quality Risk Management within GMP environments, as a practical and systematic means for determining, on a risk-basis, the scope and extent of

validation, and the likely impact of changes. As demonstrated in Chapter 6, it has been specifically designed for GMP environments, and is applicable across a broad range of GMP-related areas, activities, problems and product types.

Despite the differences between the Quality Risk Management methodology developed here and those listed above, it is not intended that this Quality Risk Management methodology would necessarily be used in a stand-alone way, in isolation from other approaches.

This research found that this methodology can be used in a synergistic manner with other Quality Risk Management methodologies and approaches, such as formal Process Mapping techniques, (which were found to be of use during Step 4 of this Quality Risk Management process, when identifying potential negative events and problems relating to system complexity and coupling), simple Cause and Effect Analysis, (which was found to be helpful when identifying the causes of potential negative events at Step 5 of the process), and Fault Tree Analysis, (which was found to be useful in determining where within the Item under Study potential negative events or failure modes should be identified and documented).

In the latter case, the author's research paper as published in the Journal of Validation Technology in February 2007 provides a detailed and practical GMP-related example of the usefulness of Fault Tree Analysis, as described above (125).

The design of this Quality Risk Management methodology also incorporates some useful concepts and learnings from the general scientific literature, not only in the field of Risk Management, but in areas such as human psychology.

For example, this methodology, like HACCP and FMEA-based methodologies, requires multi-disciplinary teams to be assembled for performing Quality Risk Management exercises. This is nothing new, and it has been a feature of Risk Management work for several decades. However, when setting out specific ground rules for team participants to follow when performing team-based activities such as brainstorming, some of the learnings gained from research in the field of cognitive and experimental psychology have been incorporated into those ground-rules. One such rule is that, during

brainstorming sessions, any opinions put forward by any team member should be considered as *hypotheses* rather than facts, so that they can be tested instead of argued against. This is based on the findings of useful research performed by Mosvick and Nelson in 1987 (132).

In addition, the simple rule that 'the majority does not rule' during team-based activities is used by this methodology, because sometimes, a single individual may be on the right track with respect to a particular issue, and others may be wrong. This is based on the work of Stamatis, as documented in his comprehensive text on FMEA titled 'Failure Mode and Effect Analysis: FMEA from Theory to Execution", 2nd edition' (44).

8.2.3.2 How the methodology adds value in relation to addressing the problems of Subjectivity and Uncertainty during Quality Risk Management exercises

During this work, problems of subjectivity and uncertainty were found to arise during the execution of Quality Risk Management exercises. Such problems were to be expected, as their existence is well documented in the scientific literature (e.g. 27, 86, 87, 89, 92, 96, 98, 100), and they are acknowledged also in ICH Q9 (9).

This research found that, when this Quality Risk Management methodology was used as an aid to qualification, validation and change control activities within GMP environments, several activities were identified that were particularly prone to problems of subjectivity and uncertainty. These activities were broadly grouped under two general headings:

- Failure Mode-related Brainstorming activities
- Activities relating to GMP Controls during Quality Risk Management exercises

A number of practical strategies were developed during this research work in order to address those concerns and difficulties. These strategies are described and discussed in detail in Chapter 5 of this thesis, and all were formally incorporated into the design of this Quality Risk Management methodology.

8.2.3.3 How the methodology adds value in facilitating Training and Educational activities for Quality Risk Management work

As discussed in Chapter 1 of this thesis, from the outset, one of the primary reasons for performing this research work related to training and educational issues.

Between the years 2002 and 2004, the pharmaceutical manufacturing industry in Ireland had, on several occasions, requested the Inspectorate Department at the Irish Medicines Board to provide guidance on the practical implications of the risk-based GMP requirements of Annex 15 to the EU Guide to GMP. During the same period, the Irish Medicines Board (IMB) had begun identifying Risk Assessment-related deficiencies during GMP inspections, and pharmaceutical manufacturing companies had, on several occasions, expressed an opinion to the IMB that additional regulatory guidance was required by Industry, in order to comply with the aforementioned risk-based requirements of Annex 15 (6).

At an Inspectorate level, at the Irish Medicines Board, and indeed at a wider European level, it was identified, particularly following the finalisation of ICH Q9 in November 2005, that training and education should be provided to Inspectors in the area of Quality Risk Management and its practical application.

This research sought to address some of those concerns, and the methodology that resulted from this work is primarily intended to serve as a practical training and educational resource for GMP Inspectors and manufacturers of pharmaceutical products, which demonstrates, at a practical level, how the risk-based requirements of Annex 15 may be complied with.

Importantly, it was not intended that this methodology would serve as *the* Quality Risk Management approach that should be used by any party, and neither the author nor the Irish Medicines Board has promoted its use within the pharmaceutical manufacturing industry, or indeed in other areas. (This point has been stated by the author repeatedly during presentations on this research.)

From the findings of this research, and from the feedback received by the author when presenting this work, it can be concluded that this methodology has added value in facilitating Quality Risk Management training and educational activities. In this regard, there is evidence that the methodology has served as a useful resource for the pharmaceutical manufacturing industry, as it works to better understand the practical application of Quality Risk Management in manufacturing. It has also been useful for GMP Inspector training activities, and it has also found application in academic institutions that are involved in the pharmaceutical-related sciences. The following paragraphs provide several examples of this.

Throughout the course of this work, a significant number of unsolicited invitations were received by the author to speak about, or to run workshops on, this approach to Quality Risk Management. Industry bodies ranging from *PhRMA*[16] in the US, the *Pharmaceutical & Healthcare Sciences Society* (formally known as the *Parenteral Society*) in the UK, to the Irish industry body *PharmaChemical Ireland,* among others, had invited the author to discuss Quality Risk Management and this approach to Quality Risk Management at their conferences or seminars. Some of those organisations invited the author to present more than once at conferences or workshops which they had organised. The feedback received by the author from all of those events was overwhelmingly positive, and Chapters 3 and 4 of this thesis provide details in this regard in relation to some of the presentations and workshops given or run by the author.

As mentioned earlier, one UK-based pharmaceutical consultancy company has found the methodology to be a useful training resource, and has confirmed that it makes reference to the methodology when providing training to pharmaceutical companies in the area of Quality Risk Management (129).

[16] PhRMA is a US pharmaceutical and biotechnology industry association. The acronym stands for *Pharmaceutical Research and Manufacturers of America*. Information on this organisation is available at www.phrma.org.

In regulatory terms, the outcomes of this research work have served as a valuable Quality Risk Management resource for GMP Inspectorates, both in Ireland and elsewhere. In Ireland, for example, this work has given the Irish Medicines Board a practical and detailed means for addressing the requests received from the Irish pharmaceutical manufacturing industry for practical guidance on the risk-based requirements of Annex 15 to the EU GMP Guide. It has also assisted the Irish Medicines Board in developing its own Risk Management policies and procedures, as required by an Irish Government *Department of Finance* directive in March 2004[17] (165).

At a more global level, the methodology developed here has served as a useful resource for the training and education of GMP Inspectors from different countries. This was demonstrated by an invitation received by the author in 2006 from the Pharmaceutical Inspection Co-operation Scheme (PIC/S) to run a detailed workshop for GMP Inspectors on the practical application of Quality Risk Management in GMP environments. (PIC/S is an organisation made up of GMP Inspectorates from various countries, whose purpose is to facilitate Inspector training and to promote compliance with GMP and related requirements.) The workshop in question was run in June 2006, at a Quality Risk Management training seminar in Düsseldorf, Germany, organised by PIC/S. This workshop, which was attended by 29 inspectors from 20 countries, and the feedback received by the author during and following it, is discussed in detail in Chapter 4 of this thesis.

The educational value of this work has become evident in several other ways also. Academic institutions involved in the teaching of pharmacy and pharmaceutical-related courses have expressed a high level of interest in this work, and some have asked to author to deliver lectures or talks on it. In 2004 and 2005, for example, the author was invited by the School of Pharmaceutical and Chemical Sciences at the Dublin Institute of Technology (DIT), to lecture on the methodology in two of its Masters Degree (MSc)

[17] This was a governmental guidance document which directed that each Irish governmental department and office was required to "initiate risk management as an integral and ongoing part of its management process", and that the Management Advisory Committees of those departments and offices should "put in place effective mechanisms to carry our risk management accordingly." (165.)

courses. These were the DIT MSc Course in *Pharmaceutical Quality Assurance* and the DIT MSc Course in *Pharmaceutical Validation Technology.*

In 2006, the author was invited by the School of Pharmacy at Trinity College, Dublin, to speak about Risk Management at its annual Qualified Person's Forum meeting in May of that year, and this was where a number of the key Quality Risk Management problem areas that were encountered during this work (such as problems of uncertainty and subjectivity) were first publicly raised by the author (166).

In terms of the broader educational value of this work, there is evidence that this research is contributing to the overall knowledge base concerning Quality Risk Management in the pharmaceutical manufacturing industry. This has been demonstrated, for example, by the acceptance for publication in 2006 and 2007 of three peer-reviewed research papers arising from this research work.

These papers were published in the US journals titled the Journal of Validation Technology and the Journal of GXP Compliance (12, 125). The 2007 Journal of Validation Technology research paper was awarded the prestigious Journal of Validation Technology *Article of the Year* award in 2007. This award was given by the Institute of Validation Technology in the US, and it was gratefully accepted by the author at the Annual Validation Conference hosted by the Institute in Philadelphia, USA, on October 25th, 2007.

The level of educational interest in those papers was such that, in 2006, the UK journal titled '*GMP Review*' requested permission to re-publish two of the three aforementioned articles. These were published in the UK in two issues of *GMP Review* in 2007 (167, 168). After their publication, the editor of *GMP Review* wrote to the author stating that the articles "were very well received, and that they were an excellent contribution to the current [Quality Risk Management] debate". (129)

In a related development, the Institute of Validation Technology in the US decided to publish a special edition handbook describing the methodology developed in this work. This handbook was titled '*GMP Training, Compliance & Risk Management Solutions: A European Perspective*' (169). The main components of this Handbook were the

aforementioned two 2006 *Journal of GXP Compliance* articles written by the author and his academic supervisor (12).

Finally, in a recent development, in mid-2007 the UK organisation known as *BARQA* (the British Association of Research Quality Assurance), which provides research support to the pharmaceutical, agrochemical and chemical industries in the UK, contacted the author to request permission to document some of this research in a Quality Risk Management-related guidance document that BARQA is planning to publish in 2008 (170). The author of that planned publication expressed a wish to present one of the practical case studies developed in this research work in that upcoming BARQA publication.

From the results of this work, and taking into account the above points, it is concluded that this methodology offers a Quality Risk Management solution that is value-adding, not only in facilitating compliance in the GMP-regulated environment with the risk-based qualification, validation and change control requirements of the EU GMP Guide, but also in facilitating Quality Risk Management training and educational activities.

8.3 Conclusions for Research Objective No. 2

Research Objective No. 2 was as follows:

To develop a practical and detailed training programme on the use of this methodology. In this regard, comprehensive training materials should be developed for facilitating training activities on the methodology, and a documented strategy should be developed for the provision of such training in a timely and resource-efficient manner.

As discussed in Chapter 6 of this thesis, throughout all parts of this research, but particularly during the various workshops that were run on this methodology, training was identified as an area that was vital in ensuring the correct use of this Quality Risk Management methodology.

This highlighted the need not only for a comprehensive training programme on the methodology to be developed, but also, there were indications that specific and detailed training materials would need to be developed on certain specific issues or features of the methodology, that warranted more detailed training. One such issue related to the way in which GMP controls are dealt with in the methodology. Another was the process used by the methodology for the identification of Potential Negative Events. A third was what to do when conflicts arise during brainstorming and other team-based activities. These and the other issues identified in this regard are discussed in detail in Chapter 6.

In response to the above and other observations, specific training strategies and materials were developed during the course of this research work in order to address the issues and difficulties identified. This resulted in the development of a comprehensive training programme on the methodology, with an associated package of training documentation and resource materials. The training programme was designed not only for trainers and potential users of the methodology, but also for both potential Team Leaders and facilitators of Quality Risk Management exercises.

Details of the training programme and all of its associated training materials were assembled and structured in the form of a *Training & User's Manual.* This was designed to provide not only materials for use during training activities on the methodology, but also, materials and guidance for use during the execution of actual Quality Risk Management exercises, for each step of the ten-step process. The structure and contents of the Training & User's Manual are discussed in detail in Chapter 6.

In relation to the need for a documented *strategy* to be developed for the provision of training on this methodology in a timely and resource-efficient manner, this was also achieved in this work.

In this regard, a number of discrete, structured and practical training activities were developed, and a formal strategy for training potential users of this Quality Risk Management methodology was devised. These practical training activities, and the training strategy that uses them, are discussed in detail in Chapter 6. To demonstrate the importance of the training strategy, it was made a key component of the actual

Quality Risk Management methodology, and it comprises one of the five elements making up the structure of the Quality Risk Management methodology.

Certain key considerations should be taken into account when a company or organisation is planning to roll out this training programme and its associated recommended training strategy. These are also discussed in detail in Chapter 6.

Based on the work presented in Chapter 6, and taking into consideration the structure and content of the Training & User's Manual that has been developed on this methodology, as well as the design of a detailed training strategy that forms part of the actual Quality Risk Management methodology, it is concluded that a practical and detailed training programme on the use of this methodology has been developed. In this regard, comprehensive training materials were developed for facilitating training activities on the methodology, and a documented strategy was also developed for the provision of such training in a timely and resource-efficient manner.

8.4 Conclusions for Research Objective No. 3

Research Objective No. 3 was as follows:

To compare the approach to Quality Risk Management developed in this work, in terms of best practice, with the application of Risk Management in two industries that can be considered to be mature and advanced in their use and application of Risk Management.

As discussed in Chapter 7 of this thesis, in order to further critically evaluate the approach to Quality Risk Management developed in this research work, it was decided to study how Risk Management has been used in other industries, and to compare the approach developed here with the Risk Management approaches used in two non-pharmaceutical industries that can be considered mature in their use and application of Risk Management methodologies. This allowed a broad assessment of the methodology to be carried out, without being constrained by GMP-related considerations and issues.

The intent of this exercise was to *benchmark* this Quality Risk Management methodology against what may be considered to be *best practice* in other, non-GMP related areas. This was so that a rounded assessment of this methodology could be made. In this regard, the aeronautics industry, as represented by the National Aeronautics and Space Administration (NASA) in the US, and the nuclear power generation industry, as represented by the Nuclear Regulatory Commission (NRC), also in the US, were selected for this best-practice benchmarking exercise.

The aeronautics and nuclear power generation industries were chosen because formal and documented Risk Management approaches and methodologies have been extensively used in those industries for over three decades. NASA and the US Nuclear Regulatory Commission were chosen as appropriate organisations within those industries for formal study, because of the extensive and open use these two organisations have made of formal and rigorous Risk Management methodologies. Also, both of those organisations are governed, and indeed empowered, by a comprehensive documented framework that formally requires the application of formal Risk Management methodologies in their day-to-day work.

The outcomes of this benchmarking exercise were positive; a comprehensive and detailed comparative study was carried out, and it was concluded that, although the approaches to Risk Management that have been developed by NASA and the US Nuclear Regulatory Commission do differ considerably in some respects to the approach to Quality Risk Management developed in this work, there were many examples of '*best practice*' strategies found that are common between the various approaches. This was especially the case in activities relating to risk identification, control and mitigation, but was true for other areas too, such as risk communication. The examples of common best practice that were identified during this comparative review exercise, as well as examples of differences in approach, are discussed in detail in Chapter 7 of this thesis.

This review also concluded that there are several useful features inherent in the NASA and NRC approaches to Risk Management that could be beneficial if incorporated into the design of the Quality Risk Management methodology developed in this work. These are also discussed in Chapter 7. Arising from that work are a number of formal

Recommendations with respect to the incorporation of such features into the design of future versions of the Quality Risk Management methodology developed in this research work. These Recommendations are listed in Section 8.5 below.

In a broader context, this comparative review exercise was beneficial in understanding where the pharmaceutical GMP environment is presently at in the evolution of risk-based work activities and regulatory requirements, as envisaged by ICH Q9. In this regard, it was concluded that, in the pharmaceutical GMP environment and its associated regulatory framework, Quality Risk Management concepts and methodologies are still at their early stages of development and adoption. In this researcher's opinion, they are nowhere near the level of development or sophistication that has been achieved by NASA and the US Nuclear Regulatory Commission in their respective regulated environments. (Detailed examples in this regard are provided in Chapter 7.)

This is not surprising, as it must be understood that ICH Q9 was only finalised in late 2005, and as result, the EU GMP environment is still at the early learning phases in its adoption of Quality Risk Management approaches. During the course of this work, the author has had opportunity to consult with many GMP Inspectors from a wide range of countries on the general level of expertise in Quality Risk Management matters that exists within EU Inspectorates. Those discussions repeatedly indicated that a comprehensive and detailed understanding among GMP inspectors of Quality Risk Management approaches and methodologies, and how they may be applied in practice, was still some way off.

Fortunately, work in this area has begun. The EEA Inspectors' Working Party, whose work is co-ordinated by the EMEA, is currently working to incorporate the principles and provisions of ICH Q9 into the EC Guide to GMP, and the Pharmaceutical Inspection Co-operation Scheme, (PIC/S), has set up an expert working group (called an *Expert Circle*) tasked with developing detailed and practical guidance for Inspectors on the practical implication of inspecting and applying Quality Risk Management approaches and methodologies within the GMP-regulatory environment. The first meeting of the PIC/S *Expert Circle on Quality Risk Management* took place in Paris in July 2007, and its work is continuing through 2008. The author is a member of that

working group.

8.5 Recommendations for Future Work

It has been approximately two years since the guidance presented by ICH Q9 was agreed and finalised by pharmaceutical regulators and industry alike. Since that time, both the industry and its regulators have been working to identify ways in which the guidance and principles of ICH Q9 may be formally incorporated into the GMP regulatory framework.

In official regulatory terms, there have not been that many definitive examples of this to draw upon up to the present time, perhaps in part because formal references to Quality Risk Management have not yet been incorporated into the EU Guide to GMP. However, one important example of how the guidance and principles of ICH Q9 have made their way into the EU GMP regulatory framework relates to an issue that has generally become known as *QP Discretion (11).*

The QP Discretion initiative was developed in response to the emergence of numerous non-compliance issues that were identified at EU-based medicinal product manufacturers in the period 2005-2006. These non-compliances, while often relatively minor in nature, had significant negative effects, as they impacted the ability of Qualified Persons (QPs) in EU-based manufacturing sites to certify and release batches of medicinal products against the information registered in EU Marketing Authorisation submissions, and this led to shortages of a range of medicinal products in Europe and in numerous other countries.

Given that many of the non-compliance issues represented deviations from the Marketing Authorisations that posed little or no risk to the safety or efficacy of the medicinal products concerned, but which led to the loss of availability of important medicinal products, a potential way forward for dealing with such non-compliances was developed in 2006 by the EEA group known as the *Heads of Medicines Agencies*

(HMA)[18]. This way forward was published by the EMEA in March 2006, in a concept paper that has become known as the Reflection Paper. It is titled: 'Reflection paper on a proposed solution for dealing with minor deviations from the detail described in the Marketing Authorisation for Human and Veterinary Medicinal products (including biological products)' (11).

The EMEA's Reflection Paper set out a proposed mechanism by which batches of a finished medicinal product with minor manufacturing or control deviations (with respect to the details set out in the Marketing Authorisation application), which posed no risk to public health, may be considered to continue to meet the requirements of the Marketing Authorisation.

At the core of this proposal was the requirement for Quality Risk Management principles to be used. The Reflection Paper required that Quality Risk Management principles be applied to the deviations concerned, and that an assessment be performed by the manufacturer using the approaches described in ICH Q9 to support a conclusion that the deviation occurrence is a minor quality deviation that does not affect the safety and efficacy of the product. The paper also required that the Quality Risk Management process used by the manufacturer is "integrated into the manufacturer's quality assurance system, notably the documentation system established to comply with GMP", and that "records are available for inspection by the Competent Authorities" (11).

The EMEA's Reflection Paper clearly demonstrated the importance and relevance of Quality Risk Management methodologies in the pharmaceutical manufacturing industry. However, as discussed in Chapter 1 of this thesis, there has been a lack of formal Quality Risk Management methodologies available for use in the GMP-regulated environment that were specifically designed for GMP-related applications. While the results of this research go some way towards addressing this problem, it would be beneficial to continue research and development work in this area, so that a *range* of Quality Risk Management methodologies and approaches can be developed that are specifically designed for application in the GMP environment.

[18] Detailed information on the composition and work of the HMA group is available at www.hma.eu.

As the pharmaceutical manufacturing industry and its regulators strive to implement and make use of the Quality Risk Management principles and guidance presented by ICH Q9 in the GMP-regulated environment, this research work has identified a number of key areas that could benefit from additional research and development work. These are presented as *Recommendations* in the sections below.

While some of the Recommendations listed below resulted from specific learnings that were made during the extensive testing and evaluation work that was performed on the Quality Risk Management methodology developed here, others resulted from the review performed during this research on the application of Risk Management in the US aeronautics and nuclear power generation industries.

8.5.1 Recommendation No. 1 - Dealing with Disagreements and Differences of Opinion during Quality Risk Management exercises

As discussed in detail in Chapter 5, disagreements and differences of opinion can occur during brainstorming sessions as part of Quality Risk Management exercises, and it is important that there are clear strategies in place for dealing with these. Several learnings were made during this research work which enabled the author to develop practical strategies in relation to dealing with disagreements and differences of opinion when they occur during brainstorming sessions. However, more work is needed in this area.

It is recommended that, as the use of formalised Quality Risk Management approaches develops in the pharmaceutical manufacturing industry, work should be performed into how best to assess the value of the opinions of team members (including experts) during brainstorming activities.

In this regard also, it is recommended that the industry should explore the potential use of formal scoring techniques (such as those developed by Brier (101) and Matheson & Winkler (102) for staff involved in making judgements during Quality Risk Management exercises. See Morgan (89) for a useful review of such scoring techniques.

8.5.2 Recommendation No. 2 - Understanding the Role played by Human Cognitive Heuristics during Quality Risk Management exercises

As discussed in Chapter 5 of this thesis, the role played by human cognitive heuristics when performing Quality Risk Management-related activities (such as estimating the probability of occurrence of an event) was an area of much concern during this research. In particular, the potential *adverse effects* of three specific heuristics on probability of occurrence estimation, expert elucidation and brainstorming in general were considered important areas to study. The heuristics in question were the heuristics of *availability*, *representativeness* and *anchoring & adjustment.*

A number of practical strategies were developed and incorporated into the design of this Quality Risk Management methodology in order to counteract the potential adverse influences of those specific heuristics. These strategies are also discussed in Chapter 5.

Notwithstanding the above, it is recommended that further research work be carried out in this area, because a comprehensive understanding is absent at this time of how the above (and other) human cognitive heuristics may affect the outcomes of Quality Risk Management exercises that are carried out in the GMP-regulated environment.

This is important considering that probability of occurrence estimation, expert elucidation and brainstorming in general are key elements of most approaches to Quality Risk Management at this time, and research has shown that these are activities that are susceptible to the adverse effects of human cognitive heuristics. Chapter 5 provides detailed information in this regard. If one were just to focus on probability of occurrence estimation activities as a starting point for such a research initiative, the potential use of probability elucidation aids in GMP environments (such as *coloured probability wheels)* as a means to counteract the adverse influences of human cognitive heuristics in this area might be a useful place to begin. For a useful discussion on such elicitation aids, see Morgan et al, pp 124-128 (89).

Focussing this recommended research work on the GMP environment would be useful in the author's opinion, because this environment is somewhat unique in the extent to which it is regulated, and a knowledge that one's opinions and decisions during Quality

Risk Management exercises may someday be questioned by GMP Inspectors may have an unanticipated affect on the human judgements that are made during such exercises.

8.5.3 Recommendation No. 3 – Making use of Near Miss Incident Information during Quality Risk Management exercises

In Quality Risk Management exercises, the use of near miss incident information, where available, has been found to be valuable when identifying potential negative events. As discussed in some detail in Chapter 7 of this thesis, this is a key element of NASA's approach to Risk Management, and one that will likely benefit the pharmaceutical manufacturing industry as well. In this methodology, Steps 4 and 5 of the Quality Risk Management process have been designed to formally require near miss incident information, where available, to be formally considered by the team performing the Quality Risk Management exercise.

The intent here is that the team must review any available near miss incident information for potential negative event signals, as well as for data on the likely causes and probabilities of occurrence of such potential negative events. Guidance in this regard has been documented and included in the Training & User's Manual on the methodology.

The use of near miss incident information is not, at this time, an activity that is widely used during Quality Risk Management exercises in the general GMP environment, and it is recommended that the pharmaceutical manufacturing industry begin efforts to promote the use of such information during Quality Risk Management exercises. This would require the formal reporting and capturing of near miss incident information within a company's Quality Management System, perhaps in a way that would be similar to how deviations are reported and captured today within GMP Quality Management Systems.

8.5.4 Recommendation No. 4 – Exploring NASA's Risk Trading and Balancing approach to Risk Control

As discussed in Chapter 7, NASA 's *Risk Trading and Balancing* approach allowed NASA to move from a strictly 'rule-based' decision-making environment of the early and mid-1990s, to one which was more risk-based, where risk was to be viewed as a resource that could be traded from one area to another within a NASA mission or project (139). NASA developed a formal Risk Management tool called the 'Risk Balancing Profile Tool' to give effect to this change in thinking (147).

This approach held that as long as there was an appropriate level of mitigation in place for risks that were accepted in a sub-system of concern within a mission or project, risks in that subsystem could be treated as a resource which could be 'traded' for risks in other sub-systems. This led NASA to accepting a higher than normal risk in one sub-system, when this was of benefit in the development of another subsystem, so that the overall mission risk could be optimised.

In this way, a balance could be reached between the risk-mitigation activities that were to be implemented in the mission or project, and the cost and schedule constraints associated with that mission or project (147). The ultimate goal of this approach was that the overall risk associated with the mission or project would be optimised and balanced against cost and scheduling constraints. In this context, several different risk mitigation strategies can be used, including making use of component redundancy strategies, designing recovery strategies into projects for high risks which were accepted, or using other types of controls, as explained in Chapter 7 (147).

Given the escalating cost of qualification and validation activities in the pharmaceutical manufacturing industry (37-39), and as the implementation of formal Quality Risk Management approaches in the Pharmaceutical industry proceeds, it is recommended that the pharmaceutical manufacturing industry should investigate how formal approaches such as NASA's *Risk Trading and Balancing* approach might help to determine when enough risk control has been exerted.

8.5.5 Recommendation No. 5 – Making use of Cost per Unit of Risk Reduction Data during Quality Risk Management exercises

At NASA, the concept of using what is known as the 'Cost per Unit of Risk Reduction' to trigger a risk mitigation process is a useful, data-driven approach. It allows NASA to evaluate and determine where best within a project or mission should the available risk mitigation resources be spent. This approach does, however, require one to either know what the cost per unit of risk reduction is in the system or sub-system of concern, or be able to calculate it.

Neither this Quality Risk Management methodology nor the majority of other Quality Risk Management methodologies used by the pharmaceutical manufacturing industry formally use *cost per unit of risk reduction* data when planning and deciding on risk mitigation activities. This is not unexpected, given that the development of Quality Risk Management in the pharmaceutical manufacturing industry is still at its early stages, and mechanisms have generally not been formally developed to calculate and apply concepts such as the cost per unit of risk reduction.

It is recommended, therefore, that formal efforts should be made in the pharmaceutical manufacturing industry to learn from NASA and others about how to calculate, monitor and apply the cost per unit of risk reduction during formal Quality Risk Management activities.

8.5.6 Recommendation No. 6 – Introducing formal Staff Competency or Certification requirements for Quality Risk Management work

It is recommended that the pharmaceutical manufacturing industry adopt a more formalised approach to developing competency or certification requirements for people performing Quality Risk Management-related activities. The competency of staff involved in risk-based decision-making will likely become an issue of concern as the industry increases its use of formalised and team-based Quality Risk Management activities. This will probably apply more to the leaders (or facilitators) of Quality Risk

Management exercises, than to the other people involved in Quality Risk Management teams.

NASA has reported that its transition to the use of more formalised Risk Management-based projects and missions was highly challenging in the area of people. Many more project teams were required, and there were defined people training needs which had not been adequately planned for. NASA stated that this was a major learning, and one for which the Agency was not prepared (141). This is a lesson that can benefit the GMP environment, as it moves towards the use of more formalised and team-based Quality Risk Management activities.

8.6 The Future Development of this Quality Risk Management methodology:

Arising out of the benchmarking exercise described in Chapter 7, in which the approach to Quality Risk Management as represented by this methodology was compared to the approaches to Risk Management as used by the US aeronautics and nuclear power generation industries, a number of potential developmental opportunities were identified for the methodology. These could be considered in any future revision of the methodology.

One of these opportunities relates to Step 10 of the Quality Risk Management process used by this methodology, which involves Risk Communication and Periodic Review activities. During the comparative review exercise, it was noted that, at NASA, the status (from a risk perspective) of all missions and projects is formally documented via what is called its *Risk Signature* programme. This involves documenting the status of the mission or project in terms of the degree of risk mitigation that has been applied to that mission or project. A simple colour-coding scheme is used by NASA to document, in a visually intuitive manner, the risk status of each mission and project. Section 7.2.3.6 of Chapter 7 provides more detailed information in this regard.

It could be of benefit to consider incorporating a similar feature into the design of the Quality Risk Management methodology developed in this work. Specifically, it would be useful if this methodology required the team performing the Quality Risk

Management exercise to formally document the overall *Qualification and Validation status* of the Item under Study at Step 10 of the process. This is currently not a feature of this methodology, but if incorporated, it would allow one to more easily translate the level of Quality Risk Management activities that have been applied to the process or item of interest directly into the Validation Master Plan for the site or project.

As at NASA, a green, yellow and red colour-coding scheme could be used as a relatively easy means of accomplishing this. This could result in colour-coded line items in the Validation Master Plan for the site or project, where the colour-coded labelling would indicate the overall status of the item listed in the Validation Master Plan, from a risk-based Qualification and Validation perspective[19].

In this regard:

- Red would indicate that no formal Quality Risk Management exercise has been performed to date on the process, facility, item of equipment, etc., listed in the Validation Master Plan.

- Yellow would mean that a formal Quality Risk Management exercise has been performed on that item, but that Risk Control, Qualification and Validation, Training, Communication and/or other actions or measures arising from that exercise have yet to be completed.

- Green labelled items in the Validation Master Plan would indicate that a formal Quality Risk Management exercise has been performed on that item, and that all actions resulting from that exercise have been completed or implemented. The next step would be for a review of the most recent Quality Risk Management exercise to be performed on the item of concern, as part of Periodic review activities.

[19] Note that any such use of colour coding in documents presupposes that the readers and users of those documents are able to differentiate between different colours. Also, there should be controls in place to ensure that the coloured labels are applied correctly.

Additionally, and as part of this developmental initiative, it would be useful if Step 10 of the Quality Risk Management process was modified to require the team to communicate to the Validation Department at the company that a) a Quality Risk Management exercise was performed on a particular process, facility, item of equipment, etc, and b) the status of such, as per the Green, Yellow and Red label definitions listed above. The idea here is that the relevant Validation Master Plan would then be updated by the Validation Department with a colour-coded risk status label next to the line item in question in the Validation Master Plan.

Another useful learning that came out of the aforementioned benchmarking exercise and which may lead to continuous improvement activities for this, and other, GMP-related Quality Risk Management methodologies concerns the issue of complexity and coupling in systems and processes.

As described in Chapter 7, much work has been carried out at NASA in an attempt to better understand the mechanisms by which failures and accidents occur. When describing the evolution of Risk Management activities at NASA, NASA's *Office of Safety and Mission Assurance* has stated that, in the past, the theory that "accidents can be prevented through good organisational design and management" was prevalent (90). However, NASA has since recognised that this approach did not work with what it calls *complex and tightly coupled* systems. As suggested by Normal Accident Theory (150), accidents and failures in such systems are inevitable. NASA has made attempts to avoid such accidents and failures by reducing (or controlling) the extent of system complexity and coupling, where possible.

NASA has demonstrated how, in complex and tightly coupled systems, failures can be the result of many seemingly unconnected causative events, and that they may result from interactions that were not in the design intent of the overall system. The accident pathways that can occur are often complex, and appear to have "an intelligence of their own, exploiting circumstances that no engineer could reasonably plan" (90). Importantly, NASA has stated that with complex systems, combinations of such events are "practically limitless", and that, these "cascading failures can accelerate out of control, confounding human operators" and denying any chance of recovery (90).

A detailed description of system complexity and coupling, and NASA's approach to dealing with it, are presented in Chapter 7.

It is not likely that the GMP environment is any more immune to the adverse effects and problems posed by system complexity and coupling than NASA has been. For this reason, it will likely be beneficial to ensure that the Quality Risk Management methodologies used within the GMP-regulated environment are capable of identifying, and/or taking into account, the extent of system complexity and coupling that may be present in the Item under Study. It is recommended that such work should be undertaken in any future developmental work performed on the Quality Risk Management methodology developed in this research work.

8.7 Final Concluding Statement

This research work has served to advance the level of knowledge in the field of Quality Risk Management for GMP applications. It has resulted in the development of a formal, readily usable, rigorous and complete Quality Risk Management methodology, designed to facilitate compliance with the risk-based qualification, validation and change control GMP requirements of the EU.

The methodology has attracted wide interest, not only from within the pharmaceutical manufacturing industry, but also from the GMP Inspectorates of several countries, from academic bodies involved in the teaching of pharmacy and pharmaceutical-related sciences in Ireland, from research journals involved in pharmaceutical science, among others. The methodology has already found application in several multinational pharmaceutical manufacturing and other companies, and has served as a valuable educational and training resource in the general application of Quality Risk Management in the GMP environment.

This work also provides a detailed trainmg programme for potential users of this methodology, and detailed training materials, as well as a documented strategy for the provision of that training have also been developed.

In a benchmarking exercise in which this approach to Quality Risk Management was compared with the application of Risk Management in the US aeronautics and nuclear power generation industries, the methodology compared very favourably, and many examples of common best practices were identified.

The application of formal Quality Risk Management methodologies in the EU pharmaceutical manufacturing industry is still at its early stages relative to other industries, and several opportunities to further develop and build upon this research work have been identified. The intention behind these recommendations for further work is to promote the continued development of Quality Risk Management methodologies and approaches within the GMP environment, so that the risks posed by medicines to patients and animals may continually be reduced and managed.

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Appendix 1

The worksheet developed for Version 3 (the penultimate Version) of this Quality Risk Management methodology

(The Worksheet is shown in the following pages.)

Important Note:

The Worksheets that were developed for Versions 1 & 2 of the Quality Risk Management methodology are presented in Chapters 2 & 3 of this thesis respectively.

The Final Version of the Worksheet (Version 4) is presented in Volume 2, Part 1, of this thesis, as one of the five components of the finalised Quality Risk Management methodology.

GMP Risk Management (RM) Exercise No: ⟶ [ ]

Step 1: Preliminary Information on the RM Exercise

Select the options below which best describe the purpose of this exercise, and fill in the relevant details:

❑ Option 1*	❑ Option 2	❑ Option 3 **
Prospective RM Exercise *	**Retrospective RM Exercise**	**Change Control RM Exercise**
The RM tool is being used to help determine, prospectively, the scope and extent of Qualification & Validation required for a new, or to be changed…	The tool is being used to help determine, retrospectively, the Qualification & Validation status of, and Qualification & Validation requirements for, a…	The tool is being used to evaluate any risks associated with a Change Control proposal relating to a…

- ❑ Manufacturing Process ***
- ❑ Cleaning & Hygiene Process ***
- ❑ Labelling & Packaging Process ***
- ❑ Training Programme
- ❑ Material Sampling Programme
- ❑ Pest Control Programme
- ❑ Stability Programme
- ❑ Preventative Maintenance Programme
- ❑ Self-Inspection Programme
- ❑ Complaints & Recall Programme
- ❑ Reduced Testing Programme
- ❑ Item of Laboratory Equipment
- ❑ Supplier / Material

*** incorporating the equipment used

- ❑ Documentation Management System
- ❑ HVAC System
- ❑ Building Management System
- ❑ Distribution System
- ❑ Supplier Approval System
- ❑ Regulatory Compliance System
- ❑ Materials Management System
- ❑ Other - specify below in this box:

❑ If the RM exercise is to help determine Qualification & Validation status or requirements in response to a **specific issue or problem** (e.g. a series of batch rejects), state the problem here:

Describe the specific issue or problem here

Notes:

* Many Prospective Risk Management Exercises will involve a Change Control, because a new or to be changed process or system, etc., will likely be managed via a Change Control. If this is the case, both Options 1 and 3 can be selected.

** In Option 3, the focus here extends beyond Qualification & Validation requirements, and considers risks associated with the Change Control in a more general way.

Step 1 Cont'd - Preliminary Information on the RM Exercise

The Item Under Study	
What is the Item Under Study? e.g. Manufacturing Process No. 1234 e.g. Dispensing Room No. 3 e.g. Upgrade to Room No. ABC e.g. New Purified Water System P2	
Boundary Details: If the Item under study has a boundary, state the boundary here. For example: • a boundary could be a P&ID for a piece of equipment or a system • it could be 2 points within a manufacturing process, within which the RM exercise applies • it could be part of a process, such as the drying & discharge stages in an API manufacturing process	
Process Map or Schematic: State the ref. no. of any map or other document which describes / maps the item under study:	
Other Document (if any) associated with Item Under Study: e.g. Cleaning SOP No. 123/4 e.g. Change Control No. 2005/11	

Reason & Relevant Background Info for this RM Exercise
State the reason this for this RM exercise, and give any background info or state any pertinent assumptions which may be relevant:

Step 2: Who's Who ... Define the Risk Management Team*

Name of RM Team Leader: Position / Area of Expertise:	

Other Team Member Name *	Position / Area of Expertise

** Note: the team should be multidisciplinary, and should possibly include personnel from QA, QC, Validation, Production, Engineering & Maintenance, Regulatory (if warranted), EHS (if warranted), & Financial (if warranted)*

****

Step 3: Review of Negative Event Probability, Severity & Detection Definitions:

Carry out the following tasks, and complete this table by ticking the appropriate options:

1. The RM Team Leader should review with the RM Team the accompanying Laminated Card, showing the default **Probability, Severity & Detection** definitions for this RM Exercise.

2. The team should then either agree to accept the default **Probability, Severity & Detection** definitions on the card, or it should define new Probability, Severity & Detection definitions for this RM Exercise.

   - ❑ **Accept** the default Probability, Severity & Detection definitions shown on the Card.
   - ❑ **Do not Accept** these default definitions, and draw up new definitions.

3. If applicable, **Document** any modified or new Probability, Severity & Detection definitions which the team has come up with, and attach these to this sheet.

   - ❑ Tick here if any new definitions are attached
   - ❑ Tick here if N/A

Step 4: What Might Go Wrong …Identify Potential Negative Events Here:

This involves compiling & reviewing data & brainstorming to identify potential negative events for the Item Under Study.

Data Review & Brainstorming Session No: ☐ Session Date: ☐

Tick One:

- ☐ Select and list below the most critical and/or complex Potential Negative Events which could be associated with the Item Under Study. (Note: No more than 3 Potential Negative Events should normally be selected for assessment.)
- ☐ If a Specific Negative Event or Problem has been identified in Step 1 for assessment, describe that below:

No.	**Examples of Potential Negative Events & Problems**	**Reference nr Notes**
	e.g. Cross Contamination Event occurs in Dryer Room No, 123 e.g. Glass in Vials of Product X → e.g. Packs of Product X are Released without a PIL e.g. Hard, yellow particles observed in batches of API X e.g. Loss of Sterility Assurance for Filling Process for Product X e.g. Low Yield Batches of API X e.g. BMS System Failure Occurs	e.g. Glass has been reported in vials of product X several times in the last year. (Ref: Complaints No. 2004/3, 6)
	Description of Potential Negative Event	**Reference or Notes**
	Description of Potential Negative Event	**Reference or Notes**
	Description of Potential Negative Event	**Reference or Notes**

Step 5: Risk Evaluation

Use a Separate Step 5 for each Negative Event. Number the controls in the format A, B, C.... etc.

Negative Event No:	**Brief Description of this Negative Event:**

List the **Potential Negative Consequences** of this Negative Event, should it occur:

Ctrl #	List any **Current Back-up Systems / Redundancy Controls** which counteract or eliminate these negative consequences should the Negative Event occur. (Note: Number each Control starting with A, B, C... etc.)

S: Severity: Rate the Severity of this Negative Event, taking into account the controls listed above, and record any necessary explanation or comments below for the Severity Rating chosen:

☐ **Critical** ☐ **Moderate** ☐ **Minor**

List the **Possible Causes or Mechanisms** for this Negative Event to Occur: **No.**	Current **Preventative** Controls in place: (*List the controls for each individual* Negative Event *Cause or Mechanism)* **Ctrl #**	**P: Prob. of Occurrence** of each cause / mechanism	**Risk** assoc. w/ each cause or mechanism **Risk=P x S** #

Instruction: For Acceptable Risks, Go to Step 8. For all other Risks, Go to Step 6

Step 6: Risk Evaluation Cont'd

This sheet is for Unacceptable or Intolerable Risks Only. Number the controls in format A, B, C.

Current Detection (D) Controls relating to Each Risk associated with Neg. Event No: [ ]

Risk #	Ctrl #	**Detection Controls** List any controls currently in place which detect the Negative Event or its consequences after the Negative Event has occurred:	**D** Detection Rating: Hi/Med/ Low/Zero	**Risk Decision Point:** Is this Risk adequately controlled? – Yes / No *i.e. Do these controls give assurance that the risk is adequately controlled & that no further controls are required? Explain Below.* **If No, Go to Step 7. If Yes, Go to Step 8**

Step 7: Risk Control

Complete only for Intolerable & Unacceptable Risks Not Adequately Controlled. One sheet per Risk.

Negative Event No:		**State the Cause or Mechanism for the Negative Event to Occur (from Step 5):**
Risk No:		
❑ Unacceptable Risk ❑ Intolerable Risk		

Risk Reduction Measures		
Ctrl #	What **New or Improved Preventative Controls** could prevent this Negative Event?	**New P Prob.** Rating for this Negative Event ❑ High ❑ Med. ❑ Low ❑ Remote
Ctrl #	What **New or Improved Back-up Systems or Redundancy Controls** could counteract the consequences of this Negative Event, should it occur?	**New S Severity** Rating for this Negative Event ❑ Critical ❑ Mod. ❑ Minor
New Risk Level = ❑ **Acceptable** - *go to Step 8* ❑ **Unacceptable / Intolerable** - *continue below*		

If the Risk is still Unacceptable or Intolerable:			
New or Improved Detection Controls **to Detect this Neg. Event?** Ctrl #		**New D Rating:**	**Risk Decision Point:**
			Is risk now adequately controlled? **Yes / No** *i.e.* *Do these controls now give assurance that the risk is adequately controlled & no further controls are required?* ❑ Yes: Go to Step 8 ❑ No: Repeat this Step Comment/Explanation:
Note: if any of the above new controls may introduce a new risk, complete a new Step 4			

Step 8: Qualification & Validation

Complete a Step 8 Worksheet for each of the controls (current and new) identified in Steps 5, 6 & 7 However, if a current control is being improved, just complete Step 8 for the improved control only.

Negative Event No:		Worksheet Step No:		Control No. (A, B, C….)		Type of Control: ❑ Current ❑ Improved ❑ New

Brief Description of the Control:

Items Required for this Control: List any items (documentation, equipment, facilities, systems or personnel resources) which are required for this control to be in place:

These Items are **Already In Place** ❑
These Items are **Not Already In Place** ❑

Complete Either Part A or B Below…

Part A: Acceptance Criteria or Required Outcomes for this Control

Are there any Acceptance Criteria or Required Outcomes associated with this Control? ❑**Yes** ❑ **No**
If yes, specify these here:

Part B: Critical Process Parameter

Does this control have any associated CPP to be measured or monitored? ❑**Yes** ❑ **No**
If yes, list the CPP below, and state the Limits / Acceptance Criteria for the CPP

Qualification & Validation Requirements

If this control has been or needs to be captured in a Qualification or Validation exercise, **describe the Qualification or Validation exercise:**

Q & V

What is the Status of this Qualification or Validation exercise?

❑ Completed
❑ Not Yet Completed
❑ N/A

Current Qualification or Validation Status of this Control: *(Tick one below)*

❑ New Qualification/Validation work needed ❑ No New Qualification/Validation work needed

Step 9: Action Items

Identify any action items from the completed Qualification & Validation Worksheets

Action Items *These could be actions to implement a control, or they could be a Qualification or Validation Exercise.*			
Negative Event Ref. No.	**Description of the Action Item:**	**Responsible Person / Group**	**Completion Target Date**

Comments or Notes:

Step 10: What are the risks, and how are we managing them

Risk Communication Activities

List any communication activities required in order to communicate risks to key groups or stakeholders

No.	*Communication Activity & Method:*	*Responsible Group:*	*Target Date:*

Periodic Review Activities:

Propose here a **Date** on which this Risk Assessment will be Reviewed: Proposed Review Date:	If there are useful **Comments or Recommendations** relating to the review of this Risk Management exercise, state those here:

Other Comments or Notes: